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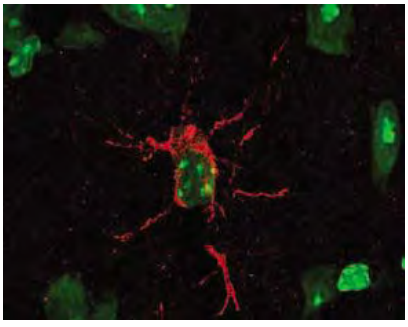
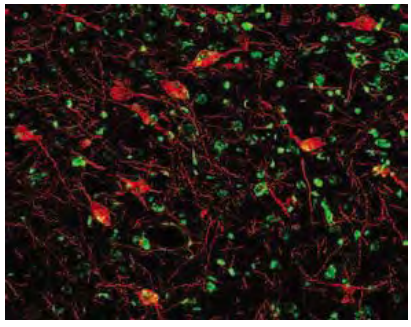


Detection of NGF Receptor in cryostat tissue sections of mouse brain using R&D Systems goat anti-mouse NGF R affinity-purified polyclonal antibody (Catalog # AF1157). Tissues were stained using Texas Red (red) and counterstained with Fluoro Nissl Green (green).



Detection of Neprilysin in cryostat tissue sections of mouse brain using R&D Systems goat anti-mouse Neprilysin affinity-purified polyclonal antibody (Catalog # AF1126). Tissues were stained using Texas Red (red) and counterstained with Fluoro Nissl Green (green).

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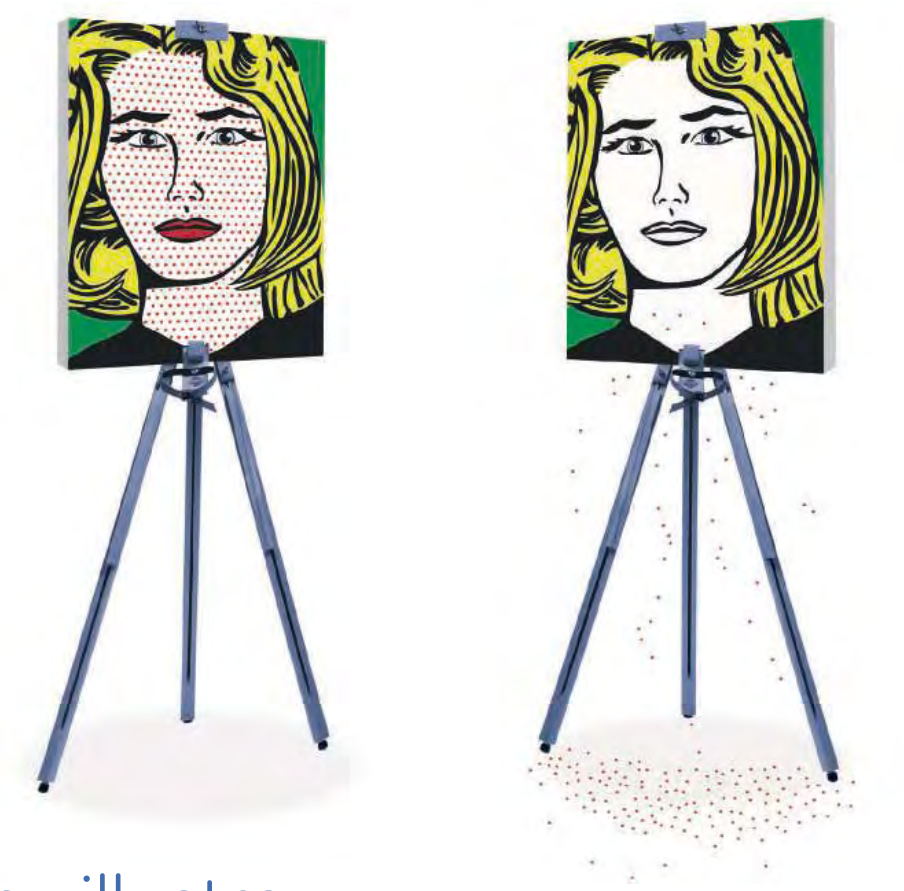

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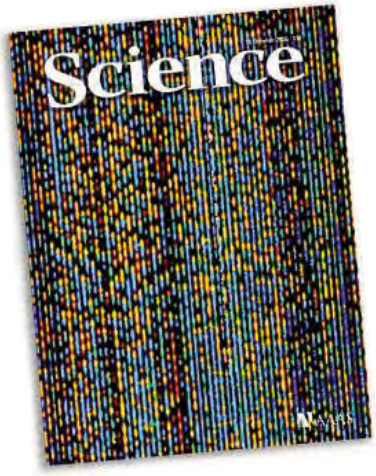


COVER

Fluorescent DNA fragments migrating through an acrylamide gel during electrophoresis. The photograph shows 65 capillaries (left to right) each containing a different sequencing reaction. Nearly 4 million such reactions were used to identify mutations in breast and colorectal cancers. See page 268.

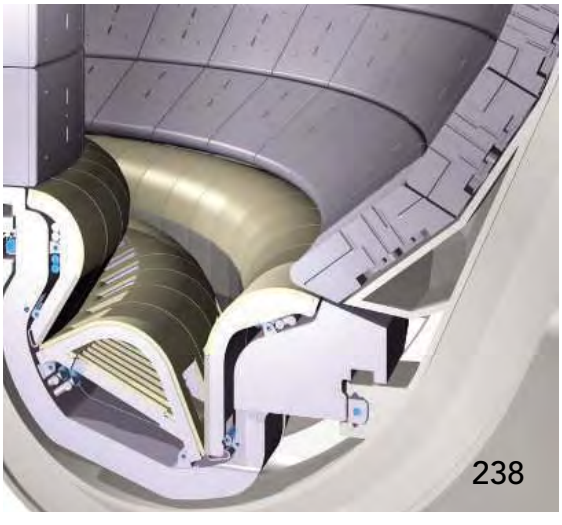
Image: D. Dressman

DEPARTMENTS

EDITORIAL

NEWS OF THE WEEK

NEWS FOCUS



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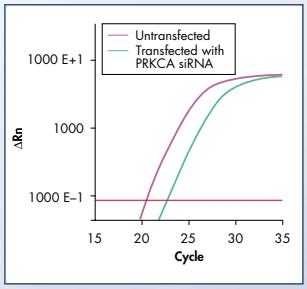
Systems Biology — RNAi and Gene Expression Analysis

GeneGlobe — the world's largest database of matching siRNAs and RT-PCR assays

New



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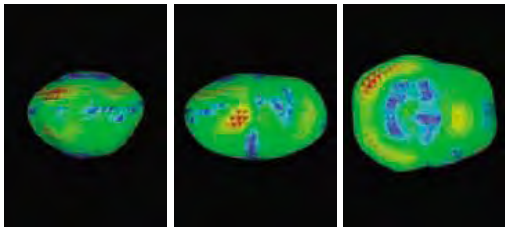

SCIENCE EXPRESS

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PLANETARY SCIENCE

Radar Imaging of Binary Near-Earth Asteroid (66391) 1999 KW4
S. J. Ostro et al.
Radar mapping shows that a large Earth-approaching binary asteroid is composed of a 0.5-kilometer asteroid orbiting a larger, unconsolidated and rapidly spinning companion.
10.1126/science.1133622

PLANETARY SCIENCE

Dynamical Configuration of Binary Near-Earth Asteroid (66391) 1999 KW4
D. J. Scheeres et al.
A binary near-Earth asteroid's shape, orbit, and rotation, which is almost rapid enough to break it apart, are the result of its recent close passage to the Sun or Earth.
10.1126/science.1133599

VIROLOGY

RIG-I–Mediated Antiviral Responses to Single-Stranded RNA Bearing 5′ Phosphates
A. Pichlmair et al.
10.1126/science.1132998

5′-Triphosphate RNA Is the Ligand for RIG-I
V. Hornung et al.
A host protein that can bind to the uncapped, single-stranded RNA genomes of many viruses triggers an antiviral response and may be a useful drug target.
10.1126/science.1132505

ASTRONOMY

The Phase-Dependent Infrared Brightness of the Extrasolar Planet υ Andromeda b
J. Harrington et al.
An extrasolar planet orbiting rapidly around a nearby star shows hot day and cold night sides, implying that little horizontal energy transport occurs in its atmosphere.
10.1126/science.1133904

BREVIA

RESEARCH ARTICLE

REPORTS

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Carl Sagan

Scientist (1934-1996)

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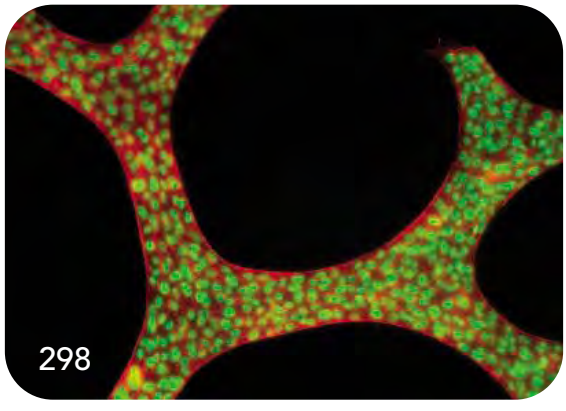

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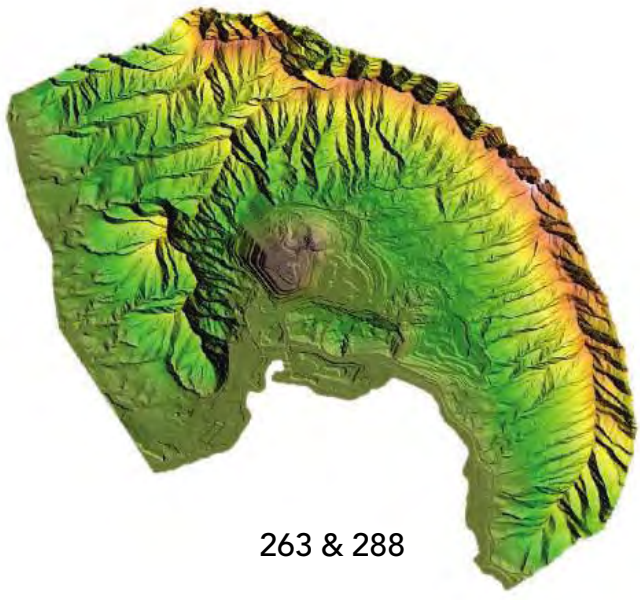

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CREDIT (LOWER LEFT IMAGE): NELSON *ET AL.*

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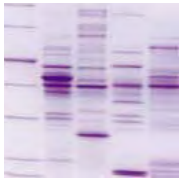

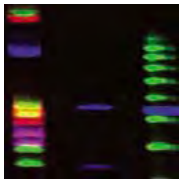

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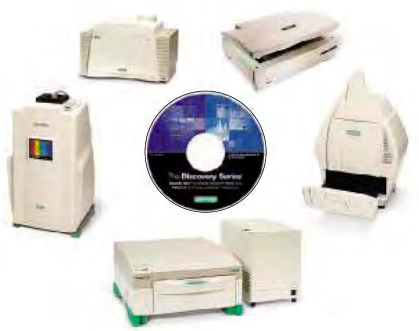

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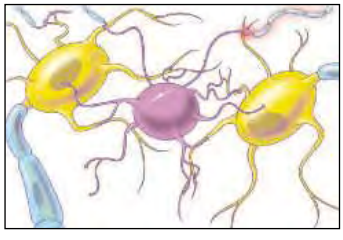

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S. J. Mulligan and B. A. MacVicar
Astrocyte swelling may trigger glutamate release, thereby influencing neuronal activity.

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J. M. Wood
Do different bacterial osmosensors use distinct mechanisms to sense osmotic pressure?

REVIEW: Regulation and Function of IKK and IKK-Related Kinases
H. Häcker and M. Karin
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EDITED BY STELLA HURTLEY AND PHIL SZUROMI

Ancient Metazoan Embryos

The Doushantuo Formation of China contains many embryos of early (Late Precambrian) metazoans. **Hagadorn *et al.*** (p. 291) have used x-ray imaging to reveal the internal structures of these embryos, which consist of a few to nearly 1000 cells. Some of the embryos show evidence of asymmetric cell division similar to many higher metazoans. None of the 162 embryos have any epithelial development, a hallmark of sponges. Instead, they are likely representative of stem-group metazoans.

Gently Arranging the Sheets

Self-assembly allows complex objects to be fabricated merely by mixing components with the right sort of surface interactions, but for small particles, a template or patterned surface is usually needed to ensure the proper ordering. **Tang *et al.*** (p. 274 show that they can assemble free-standing sheets of cadmium telluride particles in solvent without the need for surface walls or a two-solvent interface. Instead, the assembly is driven by a combination of small driving forces, such as dipole moments and hydrophobic attractions.

Timing Different Outcomes

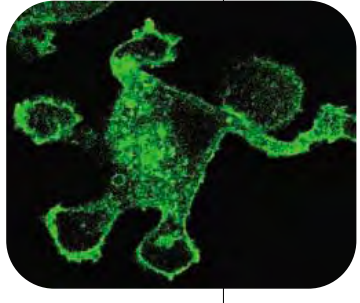
Catalysts can favor one set of products over another by reducing the energy required to reach particular conformations along one of the reaction trajectories. **Sussman *et al.*** (p. 278; see the Perspective by **Rabitz**) show that a similar effect can be induced by an intense infrared (IR) laser field in the photochemical dissociation of IBr. The reaction was initiated with a visible pulse. By applying a time delay, the IR field could be moved along the reaction trajectory, where it modified the energy landscape through Stark shifting to favor either of two pathways. The Stark pulse need not be resonant with an absorption band of the reacting molecules, so the technique should be applicable across a very wide range of substrates.

Controlling Spins in Diamond Defects

Various implementations of controlling and manipulating individual quantum states are currently being explored for possible applications in quantum information processing. **Childress *et al.*** (p. 281, published online 14 September) describe nuclear magnetic resonance experiments on individual defect centers in diamond, which acts as a single electron solid-state qubit. Using the observed spin-echo signals and extensive modeling of the hyperfine interactions, the authors reconstruct the local environment of the center and show that its electron spin coherence properties are determined by surrounding carbon-13 nuclear spins. They argue that their ability to address and manipulate electron and nuclear spins may be a possible route to quantum information processing.

The Real Deal

Truly tumor-specific molecules expressed on the cell surface are ideal targets for monoclonal antibodies in cancer therapy. **Schietinger *et al.*** (p. 304) report how a cell surface wild-type protein was transformed into a tumor-specific cancer target molecule. A mutation in a chaperone gene (Cosmc) abolished the activity of a glycosyltransferase and created novel antigenic epitope on a wild-type transmembrane protein. The combination of a monosaccharide with a wild-type protein sequence generated a syngeneic, high-affinity, highly specific, and therapeutically potent target. Mutations in the chaperone gene have also been found in patients with the autoimmune disease Tn syndrome.



Golden Origins

The origin of many hydrothermal gold deposits (those associated with magmas) has remained enigmatic: Does the gold come from the magma, or was it concentrated from the surrounding rocks, and how fast was it deposited? **Simmons and Brown** (p. 288; see the Perspective by **Heinrich**) have now obtained a direct sample of a brine emanating from a magma associated with one of the world's largest hydrothermal gold ores in Papua New Guinea. The sample, obtained via deep drilling, contains 15 parts per billion of dissolved gold. Given the flux of brine from the magma, the magma could produce the entire deposit within 50,000 years.

Cancer, One Gene at a Time

Knowing which genes are recurrently mutated in cancer cells helps illuminate the molecular pathways that underlie tumorigenesis. In a pilot study, **Sjöblom *et al.*** (p. 268; published online 7 September; see the cover and the 8 September news story by **Kaiser**) have sequenced 13,000 protein-coding genes in human breast and colorectal cancers and developed methods for distinguishing harmless sequence changes from causal mutations. Almost 200 candidate cancer genes (*CAN* genes) were mutated at significant frequency, many of which had not been previously implicated in tumorigenesis. Notably, there was little overlap of *CAN* genes mutated

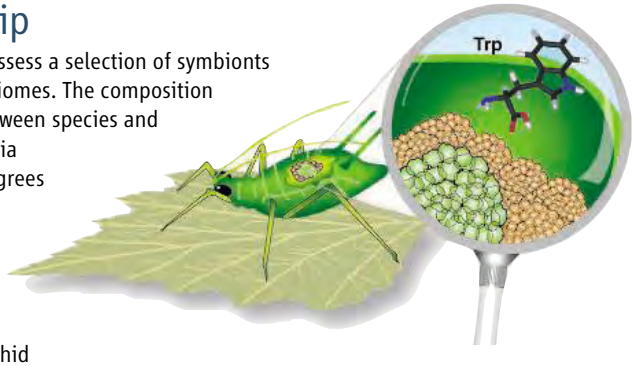
CREDITS (TOP TO BOTTOM): WHITEY HAGADORN/AMHERST COLLEGE; ANDREA SCHIETINGER

in breast and colorectal cancers, nor was there substantial overlap in different tumor specimens derived from the same tissue.

Dealing with DNA Damage

For an organism to remain healthy, cells with damaged DNA must either pause in the cell cycle for a repair job or succumb to elimination by apoptosis. **Huang *et al.*** (p. 294; see the Perspective by **Bartek and Lukas**) provide a mechanism through which cells with genomic damage may switch between these alternative fates. DNA damage activates a checkpoint signaling mechanism that arrests the cell cycle in part by inhibiting activity of cyclin-dependent kinase 2 (CDK2). The authors now find that CDK2 may also couple to the machinery controlling cell death. Normally, the transcription factor FOXO1 is phosphorylated by CDK2. In cells with extensive DNA damage, reduced phosphorylation of FOXO1 allows its translocation to the nucleus, where it enhances expression of apoptosis-inducing genes.

Failing Relationship



Aphid insect pests on plants possess a selection of symbionts in specific organs called bacteriomes. The composition of the symbiont flora varies between species and strains of aphid, and the bacteria show an intriguing range of degrees of genome reduction. **Pérez-Brocal *et al.*** (p. 312; see the Perspective by **Andersson**) have been investigating the genome of *Buchnera aphidicola* BCc, which inhabits the aphid *Cinara cedri*, along with the cohabiting secondary symbiont *Serratia symbiotica*. They found a highly reduced genome, of about 420 kilobases and 362 protein-coding genes, that is only two-thirds the size of *Buchnera* strains in other aphids. Compared with its symbiont partners, it has lost many functions. Instead, the cohabiting *Serratia* seems to have taken over the "lost" metabolic functions, and indeed, seems to be supporting the tiny genome as well as the host, which may mean that *Buchnera aphidicola* BCc has embarked on a path to extinction. In Brevia, **Nakabachi *et al.*** (p. 267) describe the limited genome of another bacterial endosymbiont, *Carsonella ruddii*.

Branching Out

At puberty, the female mammary gland is transformed from a simple epithelial tubule into an elaborate ductal tree. Underlying this global change in tissue architecture are changes in the behavior of individual cells. Certain cells within the tubules are instructed to branch, whereas their neighbors, only a few cell diameters away, are not. Using a micropatterning approach to engineer mouse mammary epithelial tubules in culture, **Nelson *et al.*** (p. 298) show that the position of branching depends on the initial tubule geometry and is determined by a local minimum in the concentration gradient of autocrine inhibitory morphogens, including transforming growth factor–β.

Rethinking Viral Resistance

In their investigations of herpes simplex encephalitis, **Casrouge *et al.*** (p. 308, published online 14 September) found that a single gene defect can impair resistance to the causative herpes simplex virus, but not others. The rare autosomal recessive mutation was present in a conserved gene encoding the endoplasmic reticulum membrane protein UNC-93B, which is thought to be involved in the cellular antiviral immune response. Cells from these subjects displayed defective response of some interferon genes, which would explain the children's severe defect in controlling viral replication. In contrast, the seemingly robust immunity of the subjects to other pathogens suggests, rather unexpectedly, that a single gene defect can lead to a pathogen-specific form of immunodeficiency.

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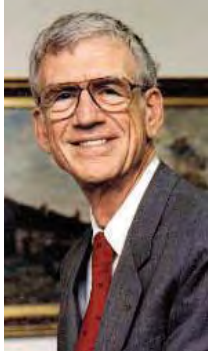

William H. Danforth is chancellor emeritus of Washington University, St. Louis, Missouri, and chairman of the board of the Donald Danforth Plant Science Center, St. Louis, Missouri.

Funding Basic Agricultural Research

A TASK FORCE ESTABLISHED BY THE U.S. DEPARTMENT OF AGRICULTURE (USDA) HAS urged that the United States modernize its management and funding of fundamental agricultural research.* As its chair, I am delighted that a bipartisan group in Congress has taken the recommendations seriously and introduced legislation to create a National Institute of Food and Agriculture (NIFA) within the USDA. NIFA will manage a new program of competitive, merit-based grants for fundamental agricultural research. We recommended first-year funding of $200 million, to grow, if successful, to $1 billion in 5 years.

The committee members all believe that advances in basic biology applied to agriculture will provide important health, environmental, and economic benefits to the United States and other nations. Increases in land productivity will contribute to preserving natural resources. Increased resistance of plants to drought and disease can help conserve precious supplies of fresh water and ensure more bountiful and predictable harvests, contributing to the global battle against hunger and poverty. Farmers are anxious for value-added products. Microbiological research should improve livestock health and help protect against pandemic transmission of animal-to-human diseases. The development of biofuels should diminish the need for petroleum, a matter of national security for many nations. In September the Bill and Melinda Gates Foundation and the Rockefeller Foundation, recognizing the opportunities, invested heavily in agricultural research programs to spur Africa's Green Revolution.

The past successes of federally funded agricultural research and education that have provided America and the world with abundant, safe, nutritious, low-cost staple grains at home and around the world do not argue for the status quo. In the past, federal funding for research has been decided by Congress on a regional basis with little or no organized scientific input.

But times change. For more than 30 years, scientific panels have been predicting that important innovations will surely come from a better understanding of the basic biology of plants and animals. The new science needed for seeking such knowledge is neither easily understood by nonspecialists nor specific to regions; drought tolerance, for example, can be studied anywhere. Accordingly, our committee urged that more grants be awarded on the basis of open competition judged for scientific merit. The NIH and the National Science Foundation have shown the way.

Past recommendations of scientific panels in agriculture have gone largely unheeded because traditional forms of research and education remain important and need funding, because Congress has been reluctant to cede some of its decision-making authority to scientists, and because other needs have taken precedence. Meanwhile, criticisms from scientific panels have encouraged those who prepare federal budgets to hold down expenditures. Today the NIH spends nearly $15 on research for every dollar spent by the USDA. The funding for competitive merit-reviewed grants is even more skewed—NIH spending for peer-reviewed research is about $120 for every dollar spent by the USDA.

Fortunately, there is growing recognition among administration officials, members of Congress, production agriculturists, and academics that modern research management and sufficient funds are needed to provide the innovations necessary to address some of our world's pressing challenges.

There is now hope that this visionary legislation will educate us all on the importance of fundamental research to agriculture and speed legislative action. Next year, Congress is set to write a new Farm Bill. I can think of no greater opportunity to make a wise investment for our farmers and our nation than to support a program of peer-reviewed research aimed at providing the knowledge for the next agricultural revolution.

–William H. Danforth

10.1126/science.1134637

* www.ars.usda.gov/SP2UserFiles/Place/00000000/NATIONAL.doc

CREDIT: JACK DYKINGA/USDA

The cricket and the fly (right).

ECOLOGY/EVOLUTION

The Advantage of Keeping Quiet

The Hawaiian Islands have long been known as a natural laboratory for studying evolution. Zuk *et al.* have assessed the effect of the selective pressure of parasitoid flies on *Teleogryllus* field crickets introduced to the island of Kauai. Female flies locate male crickets when they call to female crickets, and lay their eggs on the cricket; the larvae burrow into the host and consume it from within, eventually killing it. Over just 20 generations, the singing males dwindled in abundance owing to the selective pressure from the parasitoid, and a new, silent type of male—known as flatwings—became prevalent. Given that the song functions as a signal to potential mates, how do the flatwing males attract female partners? Field experiments suggest that the silent males congregate around the few remaining singers, increasing the chance of intercepting inquisitive females (who have possibly relaxed their requirement that the male keep singing up to the moment of mating). Thus, natural selection has not only had a rapid population genetic effect; there has been a behavioral response as well. It remains to be seen, however, if the singing males are now too rare to support the local parasitoid population, or if the singing males will disappear entirely (and, if so, whether the crickets will find a new solution to the problem of finding mates). — AMS

Biol. Lett. **2**, 10.1098/rsbl.2006.0539 (2006).

ASTROPHYSICS

Glimpsing a Magnetic Carpet

The surface of the Sun is covered in a granular network of convection cells that are created as ultrahot gas wells up from below. Intense stirring causes magnetic dipoles to grow continually within the cells before being shed into the Sun's atmosphere. By analogy with a woven textile, this distribution of magnetic loops that thread the surface has been dubbed the magnetic carpet. Despite strong theoretical underpinnings, the observational evidence for such a process has been mixed.

McIntosh *et al.* have marshaled a variety of observations from the SOlar and Heliospheric Observatory (SOHO) satellite to support the magnetic carpet model. They used ultraviolet images of the Sun dispersed into several spectral lines, including ionized silicon, neon, and carbon emissions, to trace the motions of gases at temperatures of tens of thousands to nearly 1 million K across many different cells. The gas velocities were strongest near the edges of the convection cells, and different patterns were observed in quiet Sun regions and coronal holes, consistent with the different magnetic field configurations in those environments. As the magnetic dipoles leave the cells, they release their energy through annihilation. By calculating the amount of energy released, the authors substantiate the importance of the magnetic carpet process in heating the solar corona. — JB

Astrophys. J. astro-ph/0609503 (2006).

Sb_{88} clusters added to an Sb_{300} fractal network (yellow) produce initially compact end structures (red) that flatten after further deposition (cyan).

MATERIALS SCIENCE

Films from Clusters

In the "atom by atom" growth mode of inorganic films, strain induced by the substrate can largely control the final morphology, dictating outcomes ranging from a smooth film to island formation. Carlier *et al*. have explored the consequences of delivering material to a surface as clusters rather than individual atoms. Beams of antimony clusters were tuned to peak at different average sizes—either 88 atoms (Sb_{88}) or 300 atoms (Sb_{300})—and then directed toward a graphite surface. Both types of cluster formed fractal structures on this weakly interacting substrate, but when they were deposited sequentially, distinct morphologies resulted depending on the order of addition. The large clusters, if added second, filled in the center of an Sb_{88} fractal network. In contrast, the small clusters filled out the ends of a preformed Sb_{300} network. In the latter case, further deposition of the small clusters created instability, causing the initially thick end groups to flatten out and spread along the graphite in two dimensions. The authors suggest that this transition is triggered because the strain accumulating in the compact end groups eventually exceeds the surface energy cost of producing a flatter but more crystalline structure. — PDS

Nano Lett. **6**, 1875 (2006).

GEOLOGY

Preludes to an Eruption

The cataclysmic 79 A.D. eruption of Vesuvius buried Pompeii and Herculaneum, and thanks to careful observation of the event by Pliny the Younger, marked the beginning of the science of volcanology. Several million people now live on volcanic deposits surrounding Vesuvius, and it is one of the world's most thoroughly monitored volcanoes. Thus, understanding the pre-eruptive behavior of this volcano is crucial. Morgan *et al.* have analyzed the concentration profiles of barium across crystals in the 79 A.D. ash; the profiles

reflect the time during which diffusion occurred in the magma between an abrupt phase of crystal growth or dissolution and the eruption. Because of the strong temperature dependence of the diffusion rates, the profiles also constrain the magma temperature. The data suggest that the eruptive magma was recharged several times in the decades leading up to the cataclysmic eruption, most noticeably around 20 years before. Such recharge may explain the origin of a major earthquake in 62 A.D. A separate intrusion likely triggered the eruption. — BH

Geology **34**, 845 (2006).

APPLIED PHYSICS

Patterning at a Distance

Recent experimental work has shown that a metallic, quasi–two-dimensional electron gas (q2-DEG) can be formed at the interface region of two insulators such as $LaAlO_3$ and $SrTiO_3$ when the thickness of the upper $LaAlO_3$ layer reaches a critical value of four unit cells. Because other high-mobility two-dimensional electron gases can be engineered to display a range of functional characteristics such as superconductivity, magnetism, and ferroelectric and multiferroic behavior at low temperature, there is interest in developing these oxide interfaces with the expectation of pushing such effects to higher temperature. However, because of the thinness of the upper oxide layer, conventional lithographic patterning techniques have proved detrimental to the interface properties.

Micrograph of a patterned q2-DEG (1.2 μm in diameter).

Schneider *et al.* achieve the critical thickness by lithographically patterning the q2-DEG without exposing or damaging the interface region during the process. They begin by depositing a $LaAlO_3$ layer thinner than the critical threshold onto a $SrTiO_3$ substrate, creating a temporarily insulating interface. Next they use a liftoff technique to add a thick patterned amorphous overlayer. $LaAlO_3$ height in the gaps of the amorphous layer is then increased above the critical thickness to produce a patterned, high-quality metallic q2-DEG at the buried interface. — ISO

Appl. Phys. Lett. **89**, 122101 (2006).

BIOMEDICINE

Cancer Stem Cells Lose Support

Acute and chronic myeloid leukemia (AML and CML, respectively) are maintained by populations of rare cancer stem cells that divide infrequently and therefore escape the effects of conventional chemotherapies that are designed to destroy rapidly dividing cells. Defining the properties of cancer stem cells and, in particular, identifying which of these might render the cells selectively vulnerable to therapy, are topics of great current interest.

The normal stem cells that repopulate the hematopoietic system depend on interactions with stromal elements in their bone marrow microenvironment (niche) for survival and function. To explore whether cancer stem cells are similarly dependent, Jin *et al*. treated mice carrying human AML cells with an antibody to CD44, an adhesion molecule that is overexpressed on AML cells and that is involved in cell trafficking. Disruption of CD44 function markedly reduced the growth of leukemic cells in the mice, in part because the cells failed to migrate effectively to their bone marrow niche. Independent analysis of human CML stem cells by Krause *et al*. revealed a similar dependence on CD44. Importantly, in both studies, CD44 blockade had a preferential effect on cancer stem cells versus normal hematopoietic stem cells. These results suggest that certain leukemias may respond to treatments that disrupt the interaction of cancer stem cells with their supportive surroundings. — PAK

Nature Med. **12**, 10.138/nm1483 (2006); 10.138/nm1489 (2006).

CELL BIOLOGY

Developmental Fusogen

Occasionally during development, two cells must fuse; for example, during the formation of muscle, myoblasts fuse with one another to form myotubes. This fusion of neighboring plasma membranes to form syncytia containing multiple nuclei must be very carefully regulated. The nematode *Caenorhabditis elegans* contains a number of syncytial tissues, and a protein termed EFF-1 is known to be a part of this fusion machinery. Podbilewicz *et al.* find by expression in heterologous cell lines that the EFF-1 transmembrane protein can drive the fusion of a variety of cells. The mechanism of fusion promoted by EFF-1 involves the formation of a hemifusion intermediate wherein the outer leaflets of the two plasma membranes merge before mixing of cytosolic components has occurred. For productive fusion to occur, the EFF-1 protein needs to be expressed at the surface of both partner cells, both in vitro and in intact worms. This homotypic interaction between proteins in two fusing membrane partners is a variant on the established themes in membrane fusion: In intracellular membrane fusion events, different proteins are needed in each membrane for successful fusion, whereas in virally mediated fusion, only one of the membranes needs to carry the fusogen. — SMH

Dev. Cell **11**, 471 (2006).

CREDITS: SCHNEIDER *ET AL., APPL. PHYS. LETT.* **89**, 122101 (2006)

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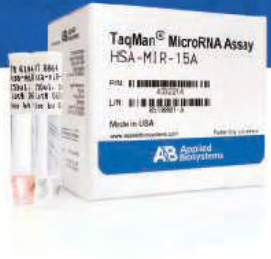

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EDUCATION

ASK, AND YE SHALL RECEIVE

A neutron star (purple, above) is a burned-out stellar husk, so why does it still glow? Are gorillas more muscular than humans because they have higher testosterone levels? To answer queries like these, the MadSci Network, a Boston-based nonprofit organization, can draw on the expertise of nearly 800 volunteer researchers around the world. The question-and-answer site has expanded from a student project at Washington University in St. Louis, Missouri, into a veritable encyclopedia that archives some 36,000 entries. Visitors from grade schoolers to professionals post up to 150 new questions a day. A cadre of scientists sifts the submissions and farms them out to the appropriate experts, who usually provide answers within 2 weeks. For example, a neutron star glows because its strong electrical field tears electrons from atoms in its outer layer, and the speeding electrons release energy. >> www.madsci.org

WEB LOGS

Graphing Lesson

Jam-packed charts that bury the main point. Cutesy layouts that make it difficult to read values from a graph. Misplaced numbers that divert the eye from the most important information. These are just some of the graphical sins Kaiser Fung enumerates in his blog Junk Charts. Once or twice a week, Fung, a statistics consultant, critiques examples from magazines, newspapers, government reports, and other sources. Although the charts typically involve business and sports topics, scientists can pick up tips about designing better diagrams for their own papers and presentations. >> junkcharts.typepad.com

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DATABASE

Ready, Set, Read

You'd be lost if you opened a mystery novel at chapter 5 instead of chapter 1. But cells don't always start at the beginning when they copy a gene into RNA. A gene can contain multiple start sites, or promoters, and which one a cell chooses can change in diseases such as cancer. For a list of these initiation sequences, check out the Eukaryotic Promoter Database, hosted by the Swiss Institute for Bioinformatics in Lausanne. The site compiles experimentally verified promoters from a host of species, including humans, nematodes, fruit flies, and cattle. Users can browse the entries or compare them to their own sequences. >> www.epd.isb-sib.ch

IMAGES

Life Through The Lens

At this new evolution timeline, the history of life unfolds in nearly 90 arresting images from renowned nature photographer Frans Lanting. Life: A Journey Through Time is a Web version of Lanting's latest book and a touring multimedia show. It features a dramatic score by composer Philip Glass. To depict critical geological and evolutionary events, the timeline showcases modern landscapes that resemble those of primordial Earth and present-day representatives of groups from diatoms to birds. For example, the ancestors of this Australian desert spadefoot toad (*Notaden nichollsi*; above) clambered onto land some 370 million years ago. >> www.lifethroughtime.com

DATABASE

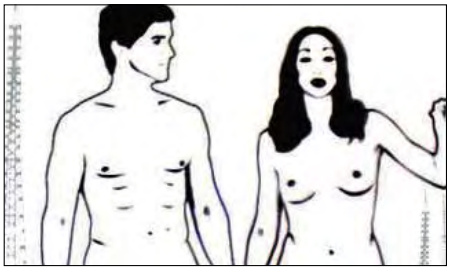
<< Neuroscience Family Tree

Rockefeller University neuroscientist Paul Greengard shared the 2000 Nobel Prize in physiology or medicine for deciphering how the neurotransmitter dopamine works in the brain. Greengard can claim more than 40 intellectual "grandchildren," and his scientific pedigree stretches back nearly 4 centuries to the German mathematician and philosopher Otto Mencke (1644–1707), who founded Germany's first academic journal. To trace mentor-protégé relationships for more than 3000 neuroscientists, climb NeuroTree, founded by postdocs Stephen David of the University of Maryland, College Park, and Ben Hayden of Duke University in Durham, North Carolina. NeuroTree differs from other projects that tease out intellectual lineages in math and chemistry (NetWatch, 24 September 1999, p. 2027; and 15 April 2005, p. 331) by allowing users to add and correct information. >> neurotree.org

CREDITS (TOP TO BOTTOM): NASA; FRANS LANTING; MICHAEL WU

GALACTIC BROADCASTING

The first-ever TV program intended for an extraterrestrial (ET) audience was sent out by the French Center for National Space Studies on 30 September from an 11-meter antenna outside Toulouse. *Cosmic Connexion*, produced and financed by the French-German ARTE channel, is now on its way to Errai, a sunlike star chosen because of its relative proximity to Earth (45 light-years) and because it has at least one planet. Couch potatoes in the Errai system with extremely advanced receivers will be able to tune in to the video in 2051.



TV hosts reach out to extraterrestrials.

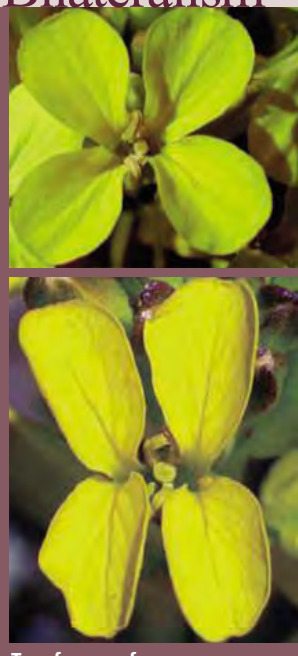
Scientists' first attempt to tell ETs about us was a 1972 plaque, containing representations of astronomy and physics as well as a naked man and woman, designed by Carl Sagan and Frank Drake for the Pioneer spacecraft. The duo hosting *CosmicConnexion* mimicked the earlier drawing by wearing only white paint. "The Pioneer couple already went into the cosmos, so they seemed like the best to send again," says co-director Anne Jaffrennou.

The $1.2 million program includes 3 hours of photos, animations, and rock videos as well as messages from ordinary earthlings collected by the producers. Says psychologist Douglas Vakoch, who advises the SETI Institute in Mountain View, California, "Even if *CosmicConnexion* fails to make contact with other worlds, it's guaranteed to help us get in better touch with what it means to be human."

Pollinators Encourage Bilateralism

All flowers can be classified into two shapes: those with radial symmetry, like the lily, and those, like the orchid, with bilateral symmetry. The first flowers had radial symmetry, but the more complex bilateral form has evolved in many species, suggesting that it is favored by natural selection.

A team led by José Gómez of the University of Granada in Spain tried to find out why by studying 300 plants of the herb *Erysimum mediohispanicum*, which has the very rare trait of producing flowers with either radial or bilateral symmetry. The team measured the three-dimensional shape of each flower using a technique called geometric morphometry, relying on 32 landmarks on petals and corolla. From thousands of observations, they determined that most visits by pollinators were made by a small beetle. Statistical analysis revealed that the flowers with bilateral symmetry were more popular with the beetles. The bilaterals were also more fit, producing more seeds and progeny over the 2-year study, the team reports in *The American Naturalist* this month.



Two forms of *Erysimum mediohispanicum*.

Risa Sargent, a plant evolutionary ecologist at the University of California, Berkeley, says Gómez and his team "make a strong case for a link between plant fitness" and bilateral symmetry. Next job: Find out the mechanism. The team speculates that the bilateral flowers offer a better "landing platform" for pollinators.

Typhoon Hits Rice Center

Heavy rains and winds gusting up to 140 km/h severely damaged greenhouses of the International Rice Research Institute (IRRI) in Los Baños, Philippines, as Typhoon Xangsane cut a swath of destruction across Southeast Asia late last month. Water flooded the homes of several staff members, causing more than $1 million in uninsured losses.

But IRRI's R&D should emerge unscathed. "We were very lucky," says spokesperson Duncan Macintosh. Although primary power was cut, a triple backup system of power generators maintained temperatures in IRRI's prize gene bank, home to most of the world's rice varieties. And the typhoon highlighted the virtues of an indigenous crop. While a maize test plot was "utterly destroyed," says Macintosh, the rice "just bounced back."

BELL LABS BUILDING SAVED

The birthplace of the cell phone and countless other high-tech innovations has been saved from the wrecking ball.

A developer was planning to raze the former Bell Labs facility in Holmdel, New Jersey, to make way for new office buildings. But when researchers got wind of the plan, they bombarded the company, Preferred Real Estate Investments Inc. in Conshohocken, Pennsylvania, with e-mails. And more than 100 members of the National Academy of Sciences, including a dozen Nobel laureates, signed a letter to the governor, the mayor, and the developer, urging the preservation of the 44-year-old building designed by Finnish architect Eero Saarinen.

The campaign worked. Last month, Preferred announced that it will refurbish the original 50,000-square-meter building, with its glass facade and transistor-shaped water tower. "These are smart people, and we sat up and listened to them," says Preferred spokesperson Scott Tattar.

Although the building will remain as office space, Bell Labs' best and brightest dispersed long ago, after the government-ordered breakup of the AT&T monopoly in 1984, notes Nobelist Douglas Osheroff of Stanford University in Palo Alto, California: "The real crime is that Bell Labs itself wasn't preserved."

CREDITS (TOP TO BOTTOM): *COSMICCONNEXION*; JÓSE GÓMEZ *ET AL.*; SOURCE: IRRI

Economics, chemistry Nobels
235 & 236

$100 million for clinical research
237

Genomics prize. An X Prize Foundation press conference last week kicked off a DNA sequencing competition that could usher in personalized medicine.

GENOMICS

On Your Mark. Get Set. Sequence!

WASHINGTON, D.C.—Leave it to J. Craig Venter to up the ante again when it comes to deciphering the human genome. Eight years ago, as head of Celera Genomics, a private company, Venter got into a DNA sequencing race with the publicly funded Human Genome Project to read our code. Now, with Venter's nudging, a new race has begun.

Last week, the X Prize Foundation announced it would pay $10 million to the first privately financed group to sequence 100 human genomes in 10 days. The winner will get another $1 million to decode the genomes of 100 additional people selected by the foundation. Physicist Steven Hawking and talk show host Larry King are already on that list. It will also include people nominated by an alliance of patient advocacy groups, foreshadowing the day when an individual's genome sequence may tailor disease treatment or prevention efforts and bringing legal and ethical issues to the forefront.

"We couldn't wait" to support this contest, says Stewart Blusson, a geologist and president of the Canadian diamond company Archon Minerals, who donated the $10 million. "It's so profound in what it means for mankind and all of life sciences."

Francis Collins, director of the National Human Genome Research Institute in Bethesda, Maryland, which has spent more than $380 million in recent years to fund new DNA sequencing technologies, also embraced the competition. Governments "can only do so much," he says. "We are delighted to see this prize."

The X Prize Foundation made headlines 2 years ago when a small aerospace company won its first award by flying a rocket into space and back twice in 10 days, demonstrating the possibility of privately funded space travel. That success intrigued Venter, head of the J. Craig Venter Institute for Genetic Research in Rockville, Maryland, who in 2003 had promised $500,000 to the first team to sequence a human genome for $1000 dollars.

In 2005, Venter joined the board of the X Prize Foundation, which revamped his challenge. Thus far, the foundation has only attracted three contestants, even though it approached about 10 groups identified in an article in *Science* as pursuing promising DNA sequencing technologies (17 March, p. 1544).

454 Life Sciences in Branford, Connecticut, and VisiGen in Houston, Texas, jumped at the chance to sign on. Steve Benner of the Foundation for Applied Molecular Evolution in Gainesville, Florida, has also joined up. But Applied Biosystems, the world's leader in DNA sequencing, and Solexa Inc. in Hayward, California, a DNA sequencing upstart, declined. "It's much more important to get the process right and get the quality right and not put on an artificial [time] constraint," says Solexa's David Bentley.

All the DNA sequencing experts polled by *Science* think a winner won't emerge for at least 5 years. The X Prize Foundation plans to offer contestants two 10-day windows each year to sequence 100 human cell lines that it provides. Those lines' DNA will have already been partially sequenced in order to verify the success of any contestant.

The rules of the game still need to be established. For example, the foundation is asking the scientific community how to define a finished genome. "I would like to see 99% of the diploid genome, i.e., about 6 billion base pairs of sequence covering both the maternal and paternal components of the chromosomes, and I would like to see 99.9999% accuracy," says Nobel laureate Hamilton Smith of the Venter Institute, a member of the prize's advisory board.

Sequencing DNA now boils down to making small DNA fragments, copying them, detecting the bases in order along each fragment, and using a computer to piece the fragments together. Vast improvements in the process will be needed to capture the prize. "We are asking for such speed that [the technology] must be able to read off fresh DNA in a massively parallel way," says Laurence Kedes, a molecular biologist at the University of Southern California in Los Angeles and co-chair of the prize advisory board.

Ewan Birney, a bioinformaticist at the Wellcome Trust Sanger Institute in Hinxton, U.K., says boosts in computational power will also be needed to assemble 100 genomes in 10 days. Currently, Birney's "farm" of 1000 computers takes a week to put a new human genome sequence together. "The data set will be closer [in volume] to what high-energy physicists have," says Birney. Still, he promises, "it's doable."

Charles Cantor, chief scientific officer of SEQUENOM Inc. in San Diego, California, predicts only groups already versed in sequencing DNA will have a chance at the prize. Others disagree. "I think it is unlikely" that the winner will come from the genome-sequencing community, says Leroy Hood, who invented the first automated DNA sequencer. And Venter predicts that the chance that someone will come out of the woodwork to scoop up the $10 million is "close to 100%." The starting gun has sounded.

–ELIZABETH PENNISI

CREDIT: ALEX WONG/GETTY IMAGES

NUCLEAR PROLIFERATION

North Korea's Bomb: Boom or Bust?

With a muffled explosion deep inside a mountain, North Korea set the world on edge this week with a claim that it had detonated a nuclear bomb. But as *Science* went to press, researchers poring over seismic signals from the blast were pondering why the detonation appears to have been so small. Some wondered whether the test was a failure—or even an elaborate hoax.

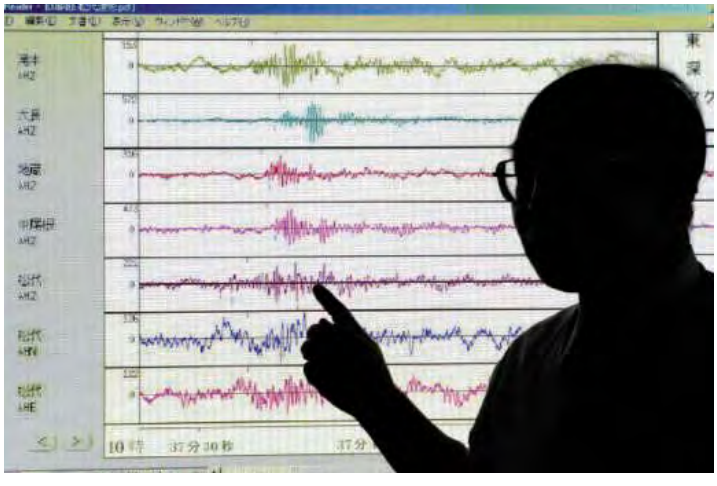
Either scenario would indicate that North Korea's claimed "nuclear deterrent" is, for now, more like a dirty bomb that would contaminate a wide area with plutonium. "The value of [the] nuclear deterrent just dropped to zero," Harvard University nonproliferation expert Jeffrey Lewis penned on 9 October on his popular blog, ArmsControlWonk.com. But the jury is still out, and the blast has sent diplomatic shock waves around the world.

The political fallout has been swift. South Korea's President Roh Moo-hyun on 9 October declared that his government "will find it difficult to stick to its engagement policy towards North Korea." China has joined Europe, Japan, and the United States in denouncing the test, paving the way for U.N.-mandated sanctions. U.S. officials insist that average North Koreans should not suffer for the sins of their government, so there is no talk of halting food aid or fuel oil shipments. But other interactions, including scientific exchanges, could be put on ice.

About the only thing known for certain is that at 10:39 a.m. local time on 9 October, a small tremor shook North Korea's North Hamgyong Province. The U.S. Geological Survey measured the event at magnitude 4.2 on the Richter scale, whereas South Korean estimates put it in the range of 3.5 to 3.7. The seismic signature—a sharp and large "P" wave relative to the "S" wave—"argues strongly that the event was an explosion," says geologist Jeffrey Park, a seismology expert at Yale University.

But the yield is unclear. That's because analysts have only a sketchy idea of the test site's geology, a critical factor in gauging yield. Assuming a tight coupling between the shock waves and surrounding rock, South Korean and Western analysts peg the blast at the equivalent of several hundred tons of TNT. (For comparison, the "Fat Man" plutonium bomb dropped on Nagasaki in 1945 was 21 kilotons.) Loose rock would dampen the shock waves, suggesting a yield of 1 to 2 kilotons, says Geoffrey Forden, a physicist and weapons expert at the Massachusetts Institute of Technology in Cambridge. That's still considerably less potent than an estimate from Russia's defense minister Sergei Ivanov, who on 9 October asserted that the blast equaled 5 to 15 kilotons of TNT.

North Korea insists it conducted a successful test. Analysts presume it was a plutonium bomb, as North Korea claims it has separated plutonium from irradiated nuclear reactor fuel and in 2004 showed a U.S. expert what appeared to be milled plutonium metal. Ever since, a debate has raged over whether North Korea has the technical prowess to get a plutonium sphere to implode and fission.



Underwhelming? A Japanese official silhouetted against seismic waves from the 9 October test.

The test, for now, does not resolve that question. Some experts say it has the hallmarks of a subcritical explosion that failed to achieve a sustained fission reaction, or perhaps only a fraction of the plutonium fissioned. If so, the North Koreans "learned they have a problem with their design, which will be helpful to them," says Thomas Cochran, nuclear program director at the Natural Resources Defense Council in Washington, D.C. Others have not ruled out the possibility of a faux nuclear test staged with conventional explosives. The only way to know for sure is if surveillance planes or aerial towers in Japan sniff out radioactive fission products in gases venting from the test shaft. If radionuclides are not detected, Park argues, "the chance of a faked test is quite high."

Bomb or no, North Korea is bracing for further sanctions—as are scientists who argue that engaging the reclusive regime will pay dividends. The Bush Administration is considering whether to classify North Korea like Cuba and bar U.S. citizens from spending money there—a de facto travel ban—except in special circumstances. And "you can forget about North Koreans getting visas to come to the United States anytime soon," predicts Matthew Bunn, a nonproliferation expert at Harvard University's Kennedy School of Government.

Such a chill would be a big mistake, argues Frederick Carriere, vice president of The Korea Society in New York City, which has helped broker contacts between U.S. and North Korean scientists. Exchanges have proven effective for promoting understanding and reconciliation, he says, and "should be maintained at all costs." But in the short term, that's unlikely to happen. Park Chan-mo, president of Pohang University of Science and Technology in South Korea, who helped organize a groundbreaking South-North science conference in Pyongyang last April, says the test is likely to scuttle follow-up meetings next month in China on university education and chemistry. "I'm very disappointed," he says. Whether authentic, dud, or outright fake, North Korea's bomb is sure to contaminate efforts to reach out to its scientists.

–RICHARD STONE

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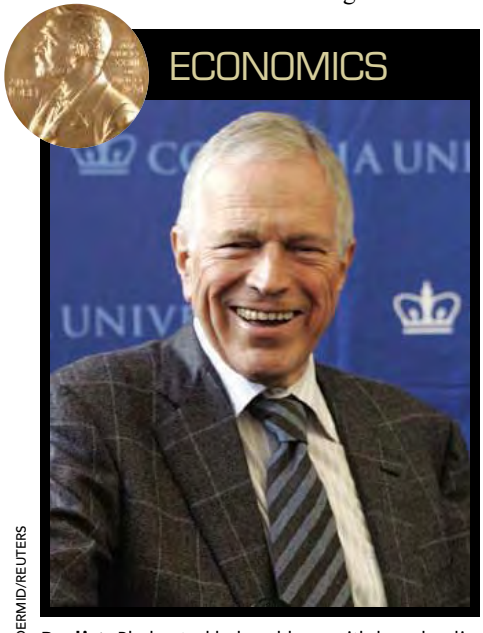
NOBEL PRIZE: ECONOMICS

Laurels for Theories That Demystified Inflation, Unemployment, and Growth

An economist who corrected a fundamental misunderstanding about the relation between unemployment and inflation has won the 2006 Nobel Prize in economics. The award completes a U.S. sweep of this year's science Nobels.

Edmund Phelps, a professor at Columbia University, receives the $1.37 million award for "his analysis of intertemporal tradeoffs in macroeconomic policy." The citation recognizes two main contributions Phelps made over a 45-year-long career: He showed that economic expansion coupled with inflation will result in only a temporary reduction in unemployment, and he determined the fraction of national income that must be saved in order to enable future generations to enjoy the same level of consumption. Both lines of research have had considerable influence on economic policy in the United States and around the world.



Realist. Phelps tackled problems with broad policy implications for modern economies.

When Phelps entered the field in the early 1960s after getting a Ph.D. from Yale University, economists believed that it was possible to cut unemployment through policies aimed at expanding the economy—such as printing more money—even though such policies would jack up inflation. Phelps realized that this macroeconomic view was divorced from the reality of how households and employers behave financially. When there's more money to go around, wages go up, and employees start spending more—leading to a short-term increase in overall employment—until they realize that prices have also been going up and that they are no better off than they were before. To offset future price rises, employees try to negotiate higher wages and scale back their demand for goods, causing employment to drop back to earlier levels. The theory, which Phelps advanced in the late 1960s, helped to explain the sorry state of the U.S. economy in the next decade when the country suffered high rates of both inflation and unemployment.

Phelps's work has had a fundamental impact on the way governments shape economic policy, says Guillermo Calvo, a professor at the University of Maryland, College Park, who was Phelps's student at Yale and then his colleague at Columbia. "The reason that the U.S. economy was able to grow rapidly in the '90s without there being high inflation was the result of fiscal and monetary policies informed by his work," Calvo says. Phelps's other work on the desirable rate of savings in an economy and the role of education and research in economic growth has had a similar influence on both economics research as well as policy, he says.

In an autobiography posted on the Web, Phelps recounts his early brush with a macroeconomic phenomenon and his natural inclination for research. His family moved from Chicago to a New York suburb in the mid-1930s after his parents lost their jobs in the Great Depression. At the age of 7, Phelps writes, he compiled a census of the cats in his apartment complex. "A few years later, I liked to spend the late afternoons by the main road recording the distribution by state of the license plates of the cars passing by." Phelps spent his teenage years digesting financial and economic news gleaned from newspapers, which he would then discuss at the dinner table with his father, who had majored in economics in college, and his mother, who had majored in home economics. The interest never faded.

"He was constantly fishing for ideas, always thinking about scientific issues," says Calvo, recalling his association with Phelps at Columbia. "If you went to him, he would always give you insights that could be used in your own research." **–YUDHIJIT BHATTACHARJEE**

CREDITS (TOP TO BOTTOM): THE NOBEL FOUNDATION; BRENDAN MCDERMID/REUTERS

Show Us the Money

PARIS—Nicolas Sarkozy, the leading conservative contender for president of France in next year's elections, has promised a research funding boost of €15 billion, or 50% more, over 5 years. But the researchers' lobby, wooed recently by other candidates (*Science*, 6 October, p. 39), pooh-poohs the offer. In an open letter to Sarkozy, Sauvons la Recherche President Bertrand Monthubert points out that Sarkozy's UMP party supports flat research funding and that Sarkozy's promise relies on heavy private sector support. "How can we believe you?" writes Monthubert. Most other candidates have vowed to increase research funds.

–BARBARA CASASSUS

Biolab Set to Open

A biosafety level 3 laboratory that Lawrence Livermore National Laboratory (LLNL) calls "critical" for U.S. security is expected to open next month at the California site. The 150-m^2 lab, which would develop biodetection technologies for civilian and military uses, has passed multiple safety reviews. But scientists are still holding their breath. A coalition of activist groups has argued that the facility requires additional environmental scrutiny (*Science*, 29 August 2003, p. 1168), and it filed a request in federal court last month to block the lab's opening. Stephan Volker, an attorney for the groups, expects that request will be denied after a 7 November hearing, as the court rejected their arguments in the larger case in 2004. LLNL won't open the lab until after the district ruling; both sides are looking ahead to the appeals court ruling, which could come at any time. **–ELI KINTISCH**

Private + Public = Progress

As companies and the government pool money, the biomedical research dollars keep on flowing. A new group called The Biomarkers Consortium last week announced that nine drug companies and several industry and patient groups have agreed to contribute $5 million, and possibly more later, for studies to find and validate markers, including genetic signatures, for diseases such as cancer, depression, and diabetes. The consortium also involves the National Institutes of Health, the Foundation for the NIH, and the Food and Drug Administration. Separately, the NIH Foundation, through another public-private group, announced $26 million in industry-funded awards for whole-genome scans for six diseases including psoriasis, schizophrenia, and kidney disease. **–JOCELYN KAISER**

NOBEL PRIZE: CHEMISTRY

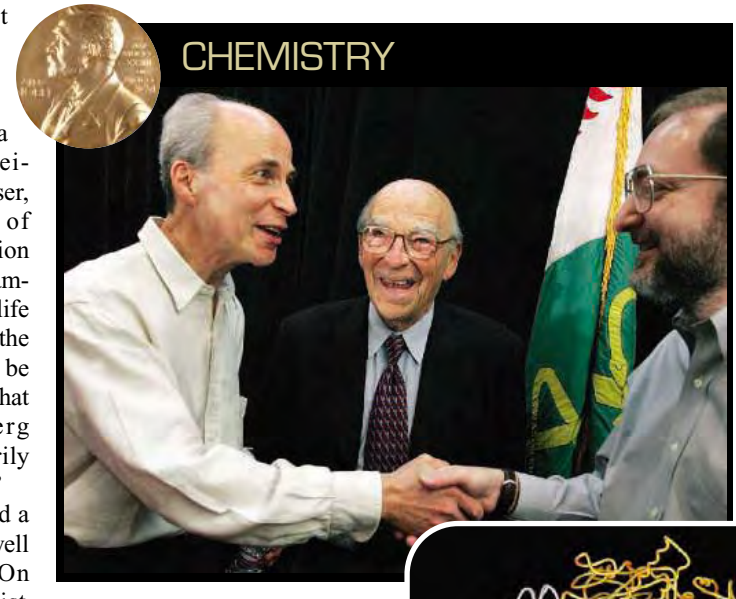
Solo Winner Detailed Path From DNA to RNA

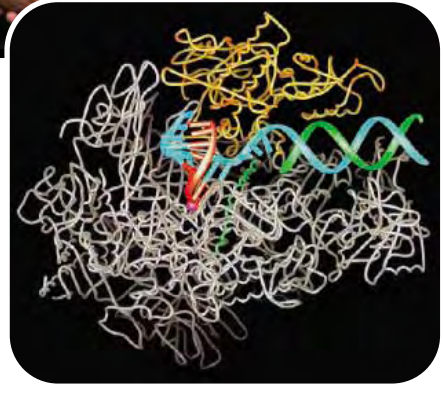
DNA to RNA to proteins. Biology's central dogma—explaining how the secrets carried in the genes are animated—was limned decades ago. But "it doesn't say anything about how it's actually done," says E. Peter Geiduschek, a molecular biologist at the University of California, San Diego. Through decades of painstaking work, Roger Kornberg, a biochemist and structural biologist at the Stanford University School of Medicine in Palo Alto, California, revealed in atomic detail the first step in this process, how DNA in cells is converted into messenger RNA, a process known as transcription. Last week, that achievement earned Kornberg a rare honor: sole possession of the 2006 Nobel Prize in chemistry.

Kornberg's work has been a "terrific contribution," Geiduschek says. Adds Peter Fraser, who heads the Laboratory of Chromatin and Gene Expression at the Babraham Institute in Cambridge, U.K., "If the secret of life could be likened to a machine, the process of transcription would be a central cog in the machinery that drives all others. Kornberg has given us an extraordinarily detailed view of this machine."

The announcement capped a banner week for Stanford as well as Kornberg's own family. On 2 October, Stanford geneticist Andrew Fire shared the physiology or medicine Nobel Prize for his part in revealing that snippets of RNA can inactivate genes (*Science*, 6 October, p. 34). Kornberg's father Arthur shared the 1959 physiology or medicine prize for helping show how DNA is copied and passed down from mother to daughter cells. The younger Kornberg was 12 years old when he accompanied his father to Stockholm. "I have felt for some time that he richly deserved it," says the senior Kornberg—an emeritus professor at Stanford—of his son's work. However, he quips, "I'm disappointed it was so long in coming." The Kornbergs are the sixth parent and child to win the Nobel Prize. Who knows, but the family could be in for further scientific accolades. One of Roger's two brothers, Tom, is a developmental biologist at the University of California, San Francisco. Ken, meanwhile is an architect specializing in part on designing research buildings. Roger Kornberg, who says he was "simply stunned" when he received the news, is slated to collect the Nobel and $1.37 million at a December ceremony in Stockholm.

When Kornberg began studying transcription in the 1960s, the notion of revealing the process on an atomic scale was "daunting," he says. By then, researchers had found the process by which the enzyme RNA polymerase transcribes genetic information in bacteria and other simple organisms known as prokaryotes.





In the genes. Stanford University structural biologist Roger Kornberg (*left*) will pick up his Nobel Prize in December, 47 years after his father Arthur (*center*). At right, pol II (gray and yellow) transcribes DNA (blue and green) into RNA (red).

But it quickly became apparent that transcription was far more complex in eukaryotes, higher organisms that include all plants and animals. To get a handle on this complexity, in the late 1980s, Kornberg's lab purified a eukaryotic transcription complex from yeast that included RNA polymerase II (pol II)—the primary transcription enzyme—and five associated proteins called general transcription factors. To their surprise, this complex didn't respond to other proteins known to activate specific genes. That discovery led them to another key molecular player known as "mediator"—a complex of some 20 proteins that relays signals from the proteins that turn on specific genes to pol II.

Kornberg wanted to use x-ray crystallography to visualize just how pol II and its partner proteins work. But that required coming up with millions of identical copies of the protein complexes so they could pack together in an ordered crystal, much like the arrangement of oranges on a store shelf. Other groups had found a way to stop pol II in the act of transcribing DNA to RNA. But that produced a mixture of RNAs, some of which turned out to be active whereas others were inactive, and that mixture wouldn't form good crystals. Separating out just one set of RNAs in the transcription machinery took 6 years. Ultimately, Kornberg's lab discovered that a blood-clotting protein called heparin binds to inactive forms of the RNA, leaving the desired ones behind. "Literally within days, we had crystals of the active RNA," Kornberg says. His team blasted those crystals with a powerful beam of x-rays and carefully mapped out how they bounced off each of the atoms. That allowed the team to construct the first-ever images of pol II in action in exquisite detail (*Science*, 20 April 2001, p. 411). Since then, Kornberg's team has produced more than a dozen related images that have revealed everything from how pol II selects the right RNA bases to how it recognizes proteins that turn on expression of specific genes.

Kornberg says one of the lab's central goals today is to produce more detailed x-ray structures of the mediator complex. "We have already got crystals of about one-third of the mediator, [from] which we believe a structure will be delivered soon," Kornberg says. That result will itself be a prize that biochemists will treasure for years to come.

–ROBERT F. SERVICE

CREDITS (TOP TO BOTTOM): JUSTIN SULLIVAN/GETTY IMAGES; ADAPTED FROM A. L. GNATT *ET AL.*, *SCIENCE* **292** (2001)

BIOMEDICINE

NIH Funds a Dozen 'Homes' for Translational Research

The National Institutes of Health (NIH) last week unveiled a key piece in Director Elias Zerhouni's plan for speeding basic research findings to the clinic: a consortium of a dozen institutions that will revamp their clinical programs to encourage more translational research.

The 12 institutions, as diverse as Columbia University and the Mayo Clinic,* received 5-year Clinical and Translational Science Awards (CTSA) totaling $108 million the first year. The program will eventually replace NIH's 50-year-old program of General Clinical Research Centers (GCRCs), which now consists of some 60 facilities with beds for patients participating in clinical studies (*Science*, 21 October 2005, p. 422).

Bench to bedside. The new consortium is meant to speed basic research findings to patients, such as this participant in a sleep study at the Children's Hospital of Philadelphia, a partner in the University of Pennsylvania's award.

To win one of the new awards, institutions agreed to create an institute, center, or department for clinical and translational research. The new entities will combine existing GCRCs with clinical training grants and programs to encourage more translational studies—for example, by exposing Ph.D. students to patient-oriented research and fostering basic clinical research teams. The CTSAs will also provide support staff, such as regulatory experts, for clinical trials. A consortium steering committee will meet regularly to work out common procedures, such as standardized informatics, so that they can share patient data for joint clinical studies. The CTSAs, says Zerhouni, illustrate "where the NIH needs to go to impact health to the greatest extent possible."

The CTSA program should make it easier to move basic findings from the lab to patients, says David Kessler, dean of the University of California, San Francisco, School of Medicine, a CTSA winner and a former commissioner of the Food and Drug Administration. "People want to do this. It's just that the barriers have been too high," he says.

One proposed condition that NIH has set aside for now is that the "homes" have the ability to appoint faculty and confer tenure, something departments usually do now. "That's going to take a while," says Anthony Hayward of the NIH National Center for Research Resources, which made the awards. For now, faculty at most CTSAs will retain their primary appointment in an academic department, he says.

NIH also awarded planning grants to 52 institutions so they can try for a future round of CTSAs. **–JOCELYN KAISER**

*For a full list, see www.ncrr.nih.gov/ncrrprog/roadmap/CTSA_9-2006.asp

STEM CELLS

California Stem-Cell Institute Unveils 10-Year Plan

Last week, the California Institute for Regenerative Medicine (CIRM) unveiled a draft of its "strategic plan" for the next 10 years. The 149-page blueprint offers timelines for initiatives from basic research to public outreach and warns that no therapies using human embryonic stem (ES) cells are likely for at least a decade.

CIRM's more modest goal, according to the plan, is to generate a "clinical proof of principle" that an ES cell therapy is able to "restore function for at least one disease." Clinical trials for two to four other diseases should be in progress, it says. And the decade should produce 20 to 30 disease-specific cell lines that illuminate genetic illnesses.

The plan lays out how CIRM will divvy up the $3 billion expected from bond sales authorized by Proposition 71. About $823 million is slated for basic research and $899 million for preclinical R&D. Clinical trials would get $656 million. The plan designates $295 million for training and $273 million for construction and renovation of labs to keep any ES cell work separate from facilities funded by the National Institutes of Health (NIH). That figure is "very modest" considering the scope of the state's research effort, worries Arnold Kriegstein, head of the Stem Cell Institute at the University of California, San Francisco (UCSF). "To encourage investigators, … we have to create environments where there's not even a hint of the possibility they're going to jeopardize their NIH support."

So far, the plan has gotten good reviews. The goals are "sensible, well-reasoned, realistic, and achievable," says stem cell researcher Evan Snyder of the Burnham Institute in San Diego, who lauds it for including training for "the next generation" of scientists. But Robert Lanza, whose company Advanced Cell Technology Inc. recently moved its headquarters to Alameda, says he's a "bit disappointed" that CIRM isn't being "more ambitious." Still, consumer groups seem reassured. The plan "shows refreshing honesty by acknowledging that it is unlikely to develop stem cell therapy for routine use during the next decade," said the Foundation for Taxpayer and Consumer Rights in Santa Monica. CIRM's governing board, the Independent Citizens' Oversight Committee, was to review the plan at a 10 October meeting and adopt a final version in December.

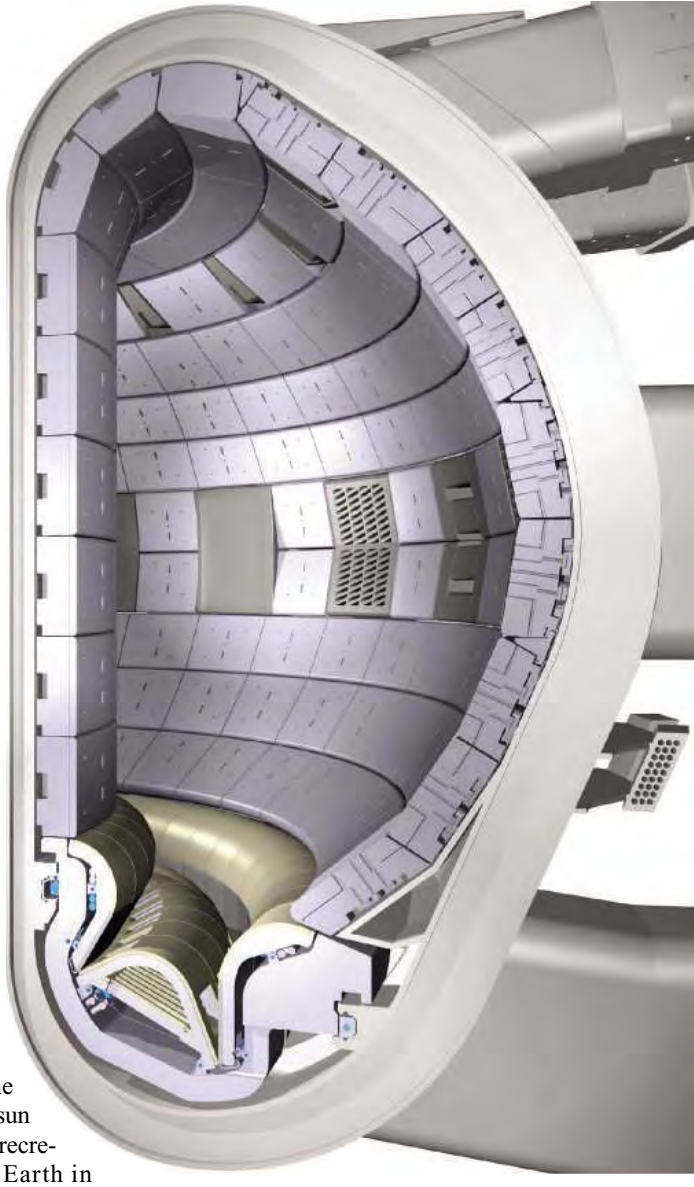
Although lawsuits have delayed the bond sale that the voters approved in November 2004, CIRM is now offering its first research grants, made possible with a $150 million loan authorized by California Governor Arnold Schwarzenegger. Kriegstein says there is hot competition for the first round of 45 grants: UCSF alone may submit as many as 41 applications.

–CONSTANCE HOLDEN

CREDIT: PHOTO COURTESY OF CHILDREN'S HOSPITAL OF PHILADELPHIA

With its big political hurdle behind it, the make-or-break project must run a gantlet of technical challenges to see whether fusion can fulfill its promise of almost limitless energy

ITER's $12 Billion Gamble



ABINGDON, U.K., AND GARCHING, GERMANY— Several times a year, hunters gather in the forests around Saint Paul lez Durance in southern France to shoot wild boar. Over the coming decade, however, a portion of their hunting ground will be cleared, and the town's cafés will gradually fill up with newcomers from San Diego and Seoul, Moscow and Munich, Naka and New Delhi. Rising out of that forest clearing will be a 20,000-tonne experiment that just might point a way out of the world's looming energy crisis.

In November, politicians representing more than half the world's population will sign an agreement that fires the starting pistol for the International Thermonuclear Experimental Reactor (ITER). Although first mooted in 1985, ITER has so far existed only on paper. The governments of China, the European Union (E.U.), India, Japan, South Korea, Russia, and the United States are now ready to hand over a $6 billion check for ITER's construction, followed by a similarly sized one for 20 years' operation. Then it is up to an international team of scientists and engineers to show that the thing will work.

If it does, the rewards could be huge. With the global population due to climb from 6.5 billion to 8.1 billion by 2030 and the economies of China, India, and others hungry for power, many new generating plants will have to be built. The choices are stark: Burn more coal, with the inevitable impact on climate; build new nuclear fission plants and deal with the radioactive waste and risk of terrorism; or try alternative sources such as solar power, although this option remains expensive and lacks efficiency.

But there is an outside bet: fusion. If it can be built, a fusion power station would emit no greenhouse gases and produce little radioactive waste, it cannot explode in a runaway reaction, and its fuel is found in seawater in virtually limitless quantities. Such a plant, unlike alternative sources, would produce the steady, reliable baseload power that cities need. And the economics are astounding: A 1-gigawatt coal-fired plant burns about 10,000 tonne of coal per day, whereas a 1-gigawatt fusion plant would need roughly 1 kilogram of deuterium-tritium fuel.

We're not even close yet, however. Indeed, skeptics joke that "Fusion is the power of the future and always will be." The sun is a gigantic fusion reactor, but recreating the conditions here on Earth in which atomic nuclei collide with such force that they fuse together has proved fiendishly difficult. A few dozen examples of the currently favored reactor design—a doughnut-shaped vessel known as a tokamak—have been built since the 1950s, but only a handful have managed to get fusion in their plasma. In 1997, the Joint European Torus (JET) in Abingdon, U.K., the biggest existing tokamak, managed to produce 16 megawatts, but that was only 65% of the power used to keep the reaction running.

By studying those earlier reactors, plasma physicists have derived scaling laws that predict that a bigger tokamak (ITER is twice the size of JET in linear dimensions) would overcome many of the problems. But ITER is not a prototype power plant; it is an experiment designed to finally decide whether taming the sun's energy to generate electricity is even viable. ITER aims to produce 500 megawatts of power, 10 times the amount needed to keep it running. But a moneymaking energy utility would need several times that amount, and it would have to keep on doing it steadily for years without a break.

ITER needs to show such performance is at least possible. But it faces many challenges: Scientists and engineers need to find a lining for its inner walls that can withstand the intense heat; they must tame the plasma instabilities that plague existing reactors; and they must find a way to run the reactor in a steady state rather than the short pulses of existing reactors. ITER must do all of this and, for the first time, maintain the plasma temperature with heat from the fusion reaction itself rather than an external source.

"There's no doubt that it's an experiment. But it's absolutely necessary. We have to build something like ITER," says Lorne Horton of the Max Planck Institute for Plasma Physics (IPP) in Garching, Germany. Researchers are reasonably confident that ITER can achieve the basic goals laid out in the project's plans, but there is less certainty about what comes after that. "I'm pretty confident ITER will work as advertised, but you can't be 100% sure," says Christopher

CREDIT: ITER

Hotter than the sun. ITER's interior must endure colossal heat loads and neutron bombardment.

Llewellyn-Smith, director of the U.K. Atomic Energy Authority's Culham Laboratory in Abingdon, home of JET. IPP's Hartmut Zohm agrees: "Certainly there's an element of risk. I'm very confident, 90-something percent, that we can produce a plasma dominated by fusion. But I'm much more uncertain that it will make a viable fusion power reactor." German physicist Norbert Holtkamp says that ITER's goal of generating excess power is clear: "Either it can do it, or it can't. If it fails, the tokamak is out."

The waiting game

The ITER project is currently in a state of limbo. Researchers nailed down the design of the reactor in 2001 after a 13-year effort costing about $1 billion. Since then, governments have been in charge. The ITER partners at that time—the E.U., Japan, and Russia (the United States had pulled out in 1999)—began negotiating who would construct which parts of the reactor. By December 2003, China and South Korea had joined the team, the United States had rejoined, a division of labor had been agreed upon, and the list of sites had been whittled down from four to two: Rokkasho in northern Japan and Cadarache, near Saint Paul lez Durance. Politicians gathered in Washington, D.C., to close the deal but failed to decide between the two sites, and the initialing of the agreement was put off (*Science*, 2 January 2004, p. 22).

Acrimonious negotiations continued for 18 months. Finally, in June 2005, a deal was struck: Japan agreed to support Cadarache, and in exchange, the E.U. will place some of its contracts with Japanese companies and will share the cost of extra research facilities in Japan (*Science*, 1 July 2005, p. 28).

Since then, negotiators have reworked the international agreement ahead of the signing next month. India has also joined, and key appointments have been made. Kaname Ikeda, a Japanese diplomat with experience of nuclear engineering, will be ITER's director general; its principal deputy director general will be Holtkamp, who managed accelerator building on the Spallation Neutron Source at Oak Ridge National Laboratory in Tennessee. Six other deputies—one from each partner apart from Japan—were appointed in July.

By the end of this year, the ITER organization will employ no more than 200 people. But across the globe, as many as 4000 researchers are already working directly or indirectly on the project, and they're itching to have some input. Fusion science has moved on in the 5 years since ITER's design was completed, and many want to make changes in the light of recent results. This generates a creative tension between the wider fusion community, which would like an adaptable machine to test as many scenarios as possible, and the ITER staff, who want the machine built on time, on budget, and ready for the next step: a power plant prototype.

"The physics community still wants modifications, all the bells and whistles. We'll always keep asking. It's healthy," says Horton. Valery Chuyanov, head of ITER's work site in Garching and now the nominee deputy director general for fusion science and technology, counters that physicists "must understand the boundary conditions. We must respect the agreement and keep within the set cost. They can't expect miracles."

Holtkamp has heeded calls for a design review and will convene a meeting in December. But, as Chuyanov points out, not everything has to be set in stone now. Contracts for big-ticket items such as the building, the vacuum vessel, and the superconducting magnets must be signed almost immediately, but other systems are years away from procurement. "The design review is not a moment in time but a continuous process," Chuyanov says.

Above all, researchers want the ITER design to be flexible. Since it was fired up in 1983, JET has had numerous transformations including the retrofitting of a divertor, a

How to Squeeze a Plasma

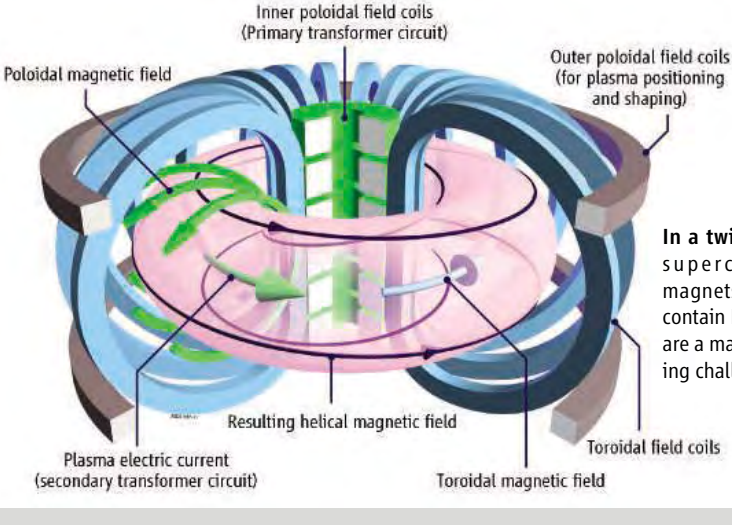
After numerous attempts during the 1940s and 1950s to find an arrangement of magnets to confine a plasma—an ionized gas—Soviet physicists Igor Tamm and Andrei Sakharov came up with the tokamak. The name derives from the Russian words for "toroidal chamber in magnetic coils."

The searingly hot plasma is kept in place by the combined effects of two magnetic fields. The first, known as the toroidal field, is generated by vertical magnetic coils ringing the vacuum vessel—in the case of the International Thermonuclear Experimental Reactor (ITER), 18 of them made from a niobium-tin superconductor. These create a field that loops horizontally through the tokamak's "doughnut."

The second, poloidal field forms vertical loops. It is generated by the plasma flowing around the torus in a current of 15 million amps. This current is itself created by electromagnetic induction: The plasma current acts as the secondary windings of a transformer, with superconducting coils in the middle of the torus acting as the primary windings. A rising current in the primary coils induces the plasma current to flow around the torus.

The combined magnetic field carves a slow spiral around the whole of the torus, and plasma particles zip around the ring in tight orbits around the spiraling magnetic field lines. The configuration keeps the particles clear of the walls and maintains a pressure in the plasma that is key to fusion.

The tokamak is not the only way to confine a plasma. Physicists are actively pursuing other schemes, such as stellarators and reverse-field pinch machines. But the tokamak is the most successful design so far and forms the basis of ITER and, most likely, the commercial power reactors that will come after it. **–D.C.**



In a twist. The huge superconducting magnets required to contain ITER's plasma are a major engineering challenge.

CREDIT: EFDA-JET

The Long Road to Fusion

1947 First kiloampere plasma created at Imperial College London.

1951 Lyman Spitzer founds Princeton Plasma Physics Laboratory and begins working on stellarator.

Early 1950s U.S., Soviet, and British doughnut-shaped fusion devices, such as ZETA at Harwell, U.K., fail to generate fusion. Most work classified.

1958 Research declassified as part of Atoms for Peace conference in Geneva.

1968 Soviet T-3 tokamak, designed by Igor Tamm and Andrei Sakharov, makes huge improvements in confinement.

1976 Joint European Torus (JET) design work begins.

1978 JET given the go ahead.

1983 JET achieves first plasma.

1985 Urged by Soviet physicists, Mikhail Gorbachev proposes international fusion project to Ronald Reagan at Geneva summit.

1988 ITER conceptual design work begins.

1992 ITER engineering design work begins.

1997 JET achieves 16 megawatts of fusion power.

structure at the bottom of the tokamak designed to siphon off waste heat and particles that is now considered essential for a tokamak. Researchers worry that if ITER's design is too fixed and the current best configuration turns out not to work, they will have little room to maneuver. "We need to maximize the flexibility of the machine. It must give enough information to build a first electricity-generating reactor. Society can't afford another intermediate step," says IPP's Harald Bolt.

Skin deep

One area in which researchers would particularly like some wiggle room is the lining of the inner surface of the vacuum vessel. This so-called first wall must be able to withstand huge heat loads: Parts of the divertor will weather as much as 20 megawatts per square meter for up to 20 seconds. In an ideal world, researchers would line their reactor with carbon: It can stand the heat and doesn't erode and pollute the plasma. But tritium in the fuel readily reacts with carbon, and the resulting radioactive hydrocarbons can be hard to shift. Nuclear licensing authorities require that all tritium must be rigorously accounted for because any released in an accident would soon enter the food chain. So tritium retention in the vessel is a major worry.

Many believe the answer to be tungsten: It has a very high melting point and low erosion. The problem is that if the plasma wobbles and strikes the surface, it would set loose tungsten ions. Because tungsten has a high atomic number, once it is stripped of all its electrons it has a huge positive charge, so even a few ions would severely dilute the plasma. As a compromise, some tokamaks have experimented with beryllium, the metal with the lowest atomic number (4, compared with tungsten's 74). But beryllium has a low melting point, so it cannot be used in areas with a large heat load, it erodes easily, and neutrons can transmute it into hydrogen or helium.

> "Either [ITER] can do it, or it can't. **If it fails, the tokamak is out.**"
>
> —Norbert Holtkamp, Principal Deputy Director General, ITER

ITER's designers have opted for a compromise: The first wall will be 80% beryllium with 5% to 7% carbon and about 12% tungsten, both concentrated in the divertor region (see diagram, p. 241). But researchers know that beryllium is just not tough enough for a generating plant and is highly toxic. "I'm convinced that at a late stage we need to convert ITER to full tungsten coverage to learn if this scenario is compatible with a power reactor," says Bolt, head of materials research at IPP.

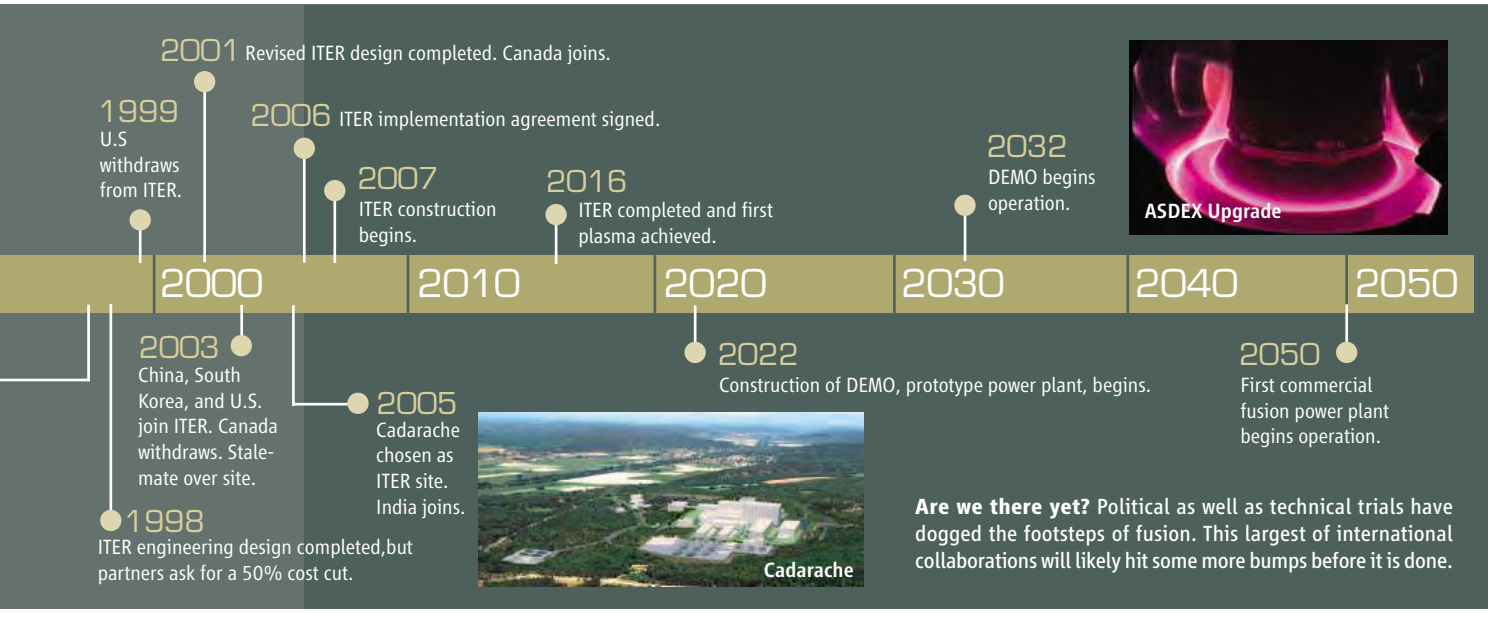
But Kimihiro Ioki, who heads the vacuum vessel and blanket division in the existing ITER organization, warns that changing the 700 square meters of the first wall would be no mean feat. The 421 panels of the main wall (excluding the divertor) together weigh more than 1 ton, and technicians would have to extract them one by one through a small port using a many-jointed mechanical arm. Ioki estimates it would take at least a year.

To run a power reactor with an all-tungsten first wall, operators would have to be sure that the plasma will behave and not touch the sides. Today, it's far from clear that researchers will be able to guarantee that. "A tokamak is the worst lab experiment you can do. It's an extremely hostile environment, and there are too many variables. It's a very difficult process to understand," says plasma physicist Steven Lisgo of the Culham lab. Phenomena at work in a tokamak range in size from micrometers to meters across, operate over time periods ranging from microseconds to years, and interact in complex nonlinear ways. It's the antithesis of a nice, clean controlled experiment, and theorists still struggle to understand everything that is going on.

Feeling the heat

In the beginning, during the 1950s, researchers thought it was going to be easy. Theorists made a calculation, based on standard random diffusion of particles, about the transport of energy and particles from the burning center of the plasma to the edge and concluded that a fusion reactor would only

CREDITS: (TOP ROW, L TO R) AP PHOTO; AFP/GETTY IMAGES; (2ND ROW, L TO R) THE SCIENCE MUSEUM/SCIENCE & SOCIETY PICTURE LIBRARY; EFDA–JET; (BOTTOM) ITER



Are we there yet? Political as well as technical trials have dogged the footsteps of fusion. This largest of international collaborations will likely hit some more bumps before it is done.

CREDITS (TOP TO BOTTOM): IPP; ITER; ILLUSTRATION: P. HUEY/*SCIENCE*, ADAPTED FROM LABORATOIRE DE PHYSIQUE DES MILIEUX IONISÉS ET APPLICATIONS (J. BOUGDIRA, R. HUGON)

need to be a half-meter across. The early machines revealed, however, that transport was actually five orders of magnitude higher because of turbulent fluctuations in the plasma. "That's why ITER has an 8-meter radius," says Zohm. Ever since those early days, the trend has been toward ever-bigger tokamaks, on the simple understanding that a larger body "cools" more slowly than a small one. And researchers have been wrestling with turbulence. "It's really difficult physics. We're only now starting to understand it," says Zohm.

In the center of the sun, the heat and pressure necessary to spark fusion come from the mass of material pressing down on the core. On Earth, we don't have the benefit of all that gravity, and a tokamak is not a strong vise (see sidebar, p. 239); ITER's plasma pressure will reach only about 5 atmospheres in the center. To compensate, the plasma has to be very hot, about 100 million kelvin. Researchers don't yet know which heating method will work best in a power reactor, so ITER will be equipped to try several, including electron beams, ion beams, neutral particle beams, and microwaves.

But as Aladdin discovered, once you fire up such a genie in a bottle, it's devilishly hard to control. Researchers have found a plethora of instabilities that cause plasma to wobble, bulge, vibrate, and generally misbehave. It's like trying to squeeze a balloon full of water: The more you squeeze, the more it bulges between your fingers. These troublesome behaviors sport exotic names such as Alfvén waves, neoclassical tearing modes, sawtooth instabilities, and resonant magnetic perturbations. The bind for researchers is that to get the most fusion power out of their tokamak, they must squeeze the balloon full of plasma as much as possible, but more pressure breeds more instabilities, which ultimately doom the fusion.

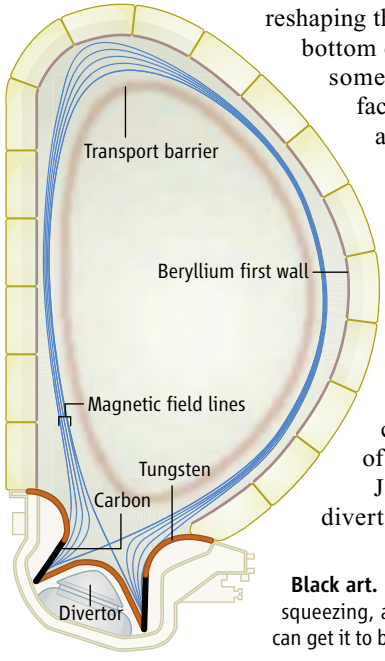
Researchers are fighting instabilities in a number of ways. One is to tweak the distribution of the plasma current flowing around the tokamak ring. Looking at a cross section of the ring, if the heating beams are used to give the current a boost in one spot here and another spot there, this can calm instabilities and allow the plasma to reach a higher pressure. "You can make very small changes in the internal current distribution, and instabilities can go away," says Zohm.

Another method is to change the shape of the plasma. In early tokamaks, the plasma was usually circular in cross section, but more modern machines have D-shaped plasmas or almost triangular ones. That helps because the magnetic surfaces that you cross as you move outward from the center of the plasma keep changing direction slightly, an effect known as "magnetic shear." "Shear suppresses [turbulent] eddies, and so transport is less efficient. It keeps energy in," says Richard Buttery of the Culham lab.

Researchers also found another way to keep plasma pressure confined when they were trying to solve a different problem: how to siphon off waste particles and heat from the edge of the plasma. When a deuterium nucleus fuses with a tritium nucleus, they produce a fast-moving helium nucleus, or alpha particle, and a speedy neutron. The neutrons are unaffected by the tokamak's magnetic fields, so they zip straight out and bury themselves in the surrounding "blanket" material, where their energy can raise steam to drive an electricity-generating turbine.

The charged alpha particles are held inside the tokamak and heat up the plasma. But once they've imparted their energy, these alphas become waste and must be removed from the plasma before they quell the fusion. In the late 1980s, researchers decided to try reshaping the magnetic field toward the bottom of the plasma vessel so that some of the outer magnetic surfaces, instead of bending round and up again, actually diverge at the bottom and pass through the vessel wall. The result is that any particles that stray out near the edge of the plasma eventually get swept down to the bottom and dumped into the divertor, a heat-resistant target where particles are cooled and then pumped out of the vessel.

JET was first fitted with a divertor in 1991. The devices are



Black art. Researchers hope that by nudging, squeezing, and bombarding the plasma, they can get it to burn hot without instabilities.

now considered indispensable because they not only remove waste but also help confine the plasma. Although researchers don't yet understand why, these open, diverging magnetic surfaces create a "transport barrier" inside the bulk of the plasma, near the edge. The pressure increases very steeply across this barrier so that the core of the plasma can be maintained at a significantly higher pressure—a configuration that plasma physicists call H-mode.

H-mode has been so successful that it is now part of ITER's baseline scenario, but it does have a downside: Running the plasma in H-mode can lead to the mother of all instabilities, known as edge-localized modes (ELMs). These happen because the transport barrier doesn't let out excess energy gradually but bottles it up until it's finally released all at once. "ELMs are not fully understood. They are bursts of power, like earthquakes," says Jerome Pamela, head of the JET project. ELMs can damage the first wall or send a blast of energy down to the divertor. Few believe that they will be able to banish ELMs altogether, but if they can be made small and regular, they are manageable. "The name of the game is to let the energy out smoothly," says Buttery.

Such is the value of H-mode that even at this late stage ITER's designers are considering design changes to cope with ELMs. One scheme investigated at JET involves injecting impurities such as nitrogen into the transport barrier to make it a bit more leaky, but this also degrades H-mode, so it is not popular. Another tactic, tested at IPP with its Asdex Upgrade tokamak, is to regularly fire pellets of frozen deuterium into the barrier. This sparks an ELM every time, keeping them steady and small. This system "will be installed" on ITER, says Chuyanov, "but is it enough? We don't know."

A late entrant into the race is a system developed in the United States using the DIII-D tokamak at General Atomics in San Diego, California. Extra magnetic coils added to the tokamak create a sort of chaotic static in the transport barrier, making it leaky enough to avoid large ELMs. "It's much simpler than pellets, more reliable," says Pamela. The problem is where to put the coils. Ideally, they would be inside the reactor vessel, close to the plasma, but that sort of reconfiguration would be one step too far for ITER's designers. "We're working very actively to find a solution for ITER, but it's impossible to put the coils inside," says Chuyanov. Researchers at JET are considering fitting them outside their vessel to see whether that might work for ITER.

Testing, testing. Engineers have already built pieces of ITER, such as this slice of vacuum vessel, to test construction.

Even if one of these techniques does tame ELMs, no one knows what will happen when ITER's self-heating regime kicks in. The fast-moving alpha particles created by fusion will have much more energy than the bulk of the particles in the plasma, and these could open up a whole hornets' nest. "This is the first time a plasma has been heated by alphas. It could create new instabilities. Experts don't think it will, but we cannot logically exclude that possibility," says Llewellyn-Smith. "That's why we need ITER," adds Zohm. "We can't simulate internal heating. It's the part we know least about."

Seeking steady state

Although there may be surprises along the way and whole new scenarios may have to be developed, few doubt that ITER will reach its goal of generating large amounts of excess power. But power is not much use commercially in bursts a few minutes long followed by a long wait while the reactor is reconfigured. Tokamaks are by their nature pulsed devices. Some of the magnetic field that confines the plasma is provided by plasma particles flowing around the tokamak—a current of some 15 million amps. This current is induced by a rising current in coils in the central hole of the tokamak ring, the coils and plasma acting like the primary and secondary windings of a transformer. But the current in the coils can't keep rising forever, so the length of any fusion run is limited. The French tokamak at Cadarache, Tore Supra, holds the record with 6-minute pulses.

But pulsed operation would put intolerable stresses on a power plant that must keep working for decades, so researchers are looking for other ways to drive the plasma current. Firing the heating beams in a particular direction will push plasma around the ring, but this will never provide all the necessary current. In the 1980s, theorists predicted another way: If the pressure gradient in the plasma is high enough, particles, which move through the plasma by spiraling around magnetic field lines, will interfere with each other in such a way as to produce a net current around the ring. This "bootstrap" current was demonstrated in the 1990s, and the Asdex Upgrade, for example, has produced as much as 30% to 40% of its current from the bootstrap effect.

Getting more bootstrap is hard because of the usual problem: It needs higher pressure gradients in the plasma, which mean more instabilities. Nevertheless, once ITER has demonstrated its baseline scenario, researchers will be aiming for an "advanced" scenario in which the induction coils are switched off and 80% to 90% of the plasma current is generated by bootstrap with the remaining push provided by heating beams. "At the very least, we will want long pulses," says Horton. But researchers don't expect the advanced scenario to be easy. "It will be a real pain to get to this," says Zohm.

Ready when you are

With a total price tag of about $12 billion, ITER is the most expensive experiment in the world apart from the international space station. Some plasma physicists are skeptical that fusion will ever be a power source on Earth and argue that we shouldn't be wasting our money on ITER. After 50 years of research, even fusion's flag-wavers concede that it may still be another half-century until we have a workable fusion power plant, but ITER researchers are undaunted. "By the middle of the century, we'll know how to do it. Then it's up to the world community to decide if they want it," says Zohm. Soviet fusion pioneer Lev Artsimovich, speaking more than 3 decades ago, had the same message. Asked when fusion power would be available, he answered, "Fusion will be ready when society needs it." That time may be fast approaching.

–DANIEL CLERY

CREDIT: ITER

PROFILE: BRIAN O'NEILL

Trying to Lasso Climate Uncertainty

An expert on climate and population looks for a way to help society avoid a "Wile E. Coyote" catastrophe

LAXENBURG, AUSTRIA—A few weeks ago, Brian O'Neill hunkered down around a table with a dozen other climate scientists in Cape Town, South Africa, to talk about the future of the planet. It was no idle speculation: Whatever they agreed upon—they knew in advance—would have clout. They were hammering out the final draft of a chapter on research methods for the massive "Fourth Assessment" of the Intergovernmental Panel on Climate Change (IPCC). The product of 3 years of consensus-building among several hundred researchers from around the world, the IPCC report is the scientific bedrock on which policymakers will negotiate everything from carbon taxes to long-term greenhouse gas targets.

But for all its authority, the IPCC exercise left O'Neill with a nagging concern: What were they leaving out? "It's important that we climate scientists speak with a single voice," he said in an interview back in his office, high up in the attic of a former Habsburg palace outside Vienna. But "the extreme scenarios that tend to fall out of the IPCC process may be exactly the ones we should most worry about," he says.

O'Neill, a climate scientist at the International Institute for Applied Systems Analysis (IIASA) here, is frustrated to see uncertainties in research used as a reason to delay action. At age 41, he is one of the youngest scientists in the IPCC network trying to reformulate climate-change projections that can cope better with uncertainty by accounting for "future learning." O'Neill hopes the strategy will make it clear that, even with gaps in understanding, it pays to act now.

His work is gaining notice. Although an American, O'Neill has scooped up one of the coveted European Young Investigator Awards (EURYI), a $1.5 million grant meant in part to keep Europe's most promising scientists at home.* "He is one of the brightest young scientists out there, and we're all watching to see what he does," says Simon Levin, an ecologist at Princeton University.

* See article on sciencecareers.org (sciencecareers.sciencemag.org/career_development/previous_issues/articles/2006_10_13/an_ambitious_effort_to_plug_europe_s_research_gap).

CREDIT: PROVIDED BY B. O'NEILL

A winding path

O'Neill's job is to predict the future, but his own career path has been unpredictable. With 3 years' training in engineering and a degree in journalism, he became passionately involved in the 1980s in efforts to prevent ozone depletion, working for Greenpeace in California. After collecting a Ph.D. in earth-system sciences from New York University, he did research stints at Brown University and the Environmental Defense Fund in New York City.

In 2002, he moved to IIASA, a center for multidisciplinary research founded in 1972. Here, O'Neill has built up a new program focusing on population and climate change. The treatment of demographics in most climate-change analyses, he says, is "simplistic at best." With the EURYI money, he's assembled a team of a half-dozen demographers, economists, statisticians, and physical scientists to sharpen the models.

Futurist. Brian O'Neill and his group think big improvements are needed in estimates of China's role in climate change.

A long-limbed basketball player who looks like he could be fresh out of graduate school, O'Neill seems to peel away layers of uncertainty as he speaks. His slow-paced answers to questions often begin with a detailed preamble of assumptions, conditions, and footnotes. But as the father of two daughters, he says, "thinking about how the world will be in 50 years is not so abstract for me anymore."

At IIASA, his work focuses on building realistic demographic projections, and China has become his main beat. Different predictions of how the country's population will age and urbanize—and how carbon-emission policies will shape Chinese consumption—have an enormous effect on global climate change scenarios. But obtaining accurate demographic data has been difficult. With the help of a Chinese member of his new team, O'Neill has done an analysis revealing that the IPCC assumptions about China's rate of urbanization and energy consumption could be off by a factor of 2.

Learning about learning

Earlier this year, O'Neill organized a unique meeting at IIASA, bringing together experts from different areas of climate science, economics, and demography to think about how they generate knowledge. One of the most important questions that emerged, says Klaus Keller, a climate scientist at Pennsylvania State University in State College, is how do you avoid "the Wile E. Coyote effect?" The cartoon coyote often doesn't realize he's falling off a cliff until he looks down, too late to turn back. One of the potential cliffs in climate change involves the ocean's conveyer-belt system—known as the meridional overturning circulation (MOC)—which prevents a Siberian chill from spreading across western Europe by carrying warm water north from the equator. Scientists worry that global warming could abruptly change or even shut down the MOC. "These are the kind of climate thresholds that we need to identify," says Keller.

Scientists need to know more about the natural variability in MOC behavior, says O'Neill. But they don't even know "how precise your measurements have to be" or how large an area must be studied

before uncertainty could be sufficiently reduced to spot "the edge of the cliff." He argues that the only way to attack such complex uncertainties with limited time and resources is to have scientists from different fields work together, assessing observations over many years to learn which approaches pay off the most. O'Neill and others did exactly this with 2 decades of research on the carbon cycle, finding that some kinds of observations narrowed uncertainty in model parameters far better than others. Such big-picture, multidisciplinary studies are low on the priority scale of funding agencies, but this is exactly what's needed if you want "to learn about the potential of an MOC shutdown," he says.

The second big question to emerge from the IIASA sessions is how can we tell if mainstream research is headed in the wrong direction? O'Neill, Michael Oppenheimer, and Mort Webster, climate scientists at Princeton and the Massachusetts Institute of Technology in Cambridge, respectively, use the term "negative learning" to describe cases in which scientific consensus builds around the wrong model. "This is what happened with ozone," says Oppenheimer. People believed that ozone's key interactions are with other gases, until scientists realized that the critical reactions driving ozone depletion occur on the surfaces of airborne particles. With revised reaction rates, it was suddenly clear that the planet's protective ozone layer was in much bigger trouble than had been thought. Oppenheimer proposes that scientists team up with philosophers and historians to find common signs of negative scientific learning. A search for such red flags could be built into climate science's regular review process. And O'Neill says more funds should be set aside to explore hypotheses outside the mainstream.

Modelers' home. A Habsburg palace near Vienna is inhabited by IIASA scientists.

Researchers desperately need a strategy for tackling climate uncertainties, O'Neill says. Michael Schlesinger, a climate scientist at the University of Illinois, Urbana-Champaign, points to another example. Polar ice sheets are melting more rapidly than anticipated, and some observers fear that this could lead to a catastrophic sea-level increase (*Science*, 24 March, p. 1698). "Things are happening right now with the ice sheets that were not predicted to happen until 2100," Schlesinger says. "My worry is that we may have passed the window of opportunity where learning is still useful."

Whether a catastrophe can be averted using some form of scientific introspection—or learning about learning, as O'Neill calls it—remains unclear. The concept, like O'Neill's career, is still at an early stage of development.

–JOHN BOHANNON

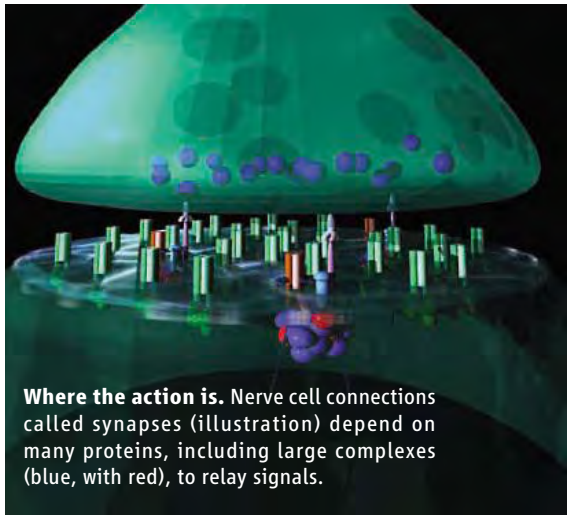
NEUROSCIENCE

Brain Evolution on the Far Side

Over evolutionary time, the protein portfolio of the receiving side of the synapse has become more sophisticated—could that be why brains got bigger and smarter?

Mind the gap. To Londoners, that phrase, which warns subway commuters to be careful stepping off platforms onto trains, has become such a cliché that it's emblazoned on T-shirts and posters. But to Seth Grant, who works at the Wellcome Trust Sanger Institute in Hinxton, just an hour or so north of London, it's an apt summation of his research focus.

After years of studying the 10- to 50-nanometer gaps between nerve cells called synapses, Grant is convinced that a key to the evolution of the brain lies within these crucial connections. The human brain relies on a quadrillion synapses to connect its circuitry, and Grant has been comparing, in species big and microscopic, the protein milieu of the synapse's far side, the portion that receives another neuron's signals.



Where the action is. Nerve cell connections called synapses (illustration) depend on many proteins, including large complexes (blue, with red), to relay signals.

As nerve cells fire, the transmitting neuron quickly releases chemicals called neurotransmitters—the release takes about 200 microseconds in the giant squid—that zip across the synapse to another nerve cell's membrane. That "postsynaptic" membrane is awash with cell surface receptors and signaling molecules standing by to relay incoming signals throughout the cell. And with some 1100 proteins, says Grant, "the most molecularly complex structure known [in the human body] is the postsynaptic side of the synapse."

Grant maintains that these proteins hold new clues about the evolution of the brain. He has found major species differences among the protein content of the postsynapse, disparities that could help explain, for example, the improved cognitive capacities of vertebrates. "Maybe synapse protein evolution has been more important than [increases in] brain size," says Grant.

His work also suggests that neurobiological research with invertebrates is less relevant to the human brain than researchers have assumed. "The textbook version is that a synapse is the same thing in a human and a slug," says Svante Pääbo, a molecular geneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. "[Grant] shows that that is not likely to be the case."

Many evolutionary biologists attribute the unique properties of the human brain to its relatively large size and complex cortex. But Grant thinks that ever-more-intricate molecular interactions within synapses have made possible the circuitry that underlies our ability

CREDITS (TOP TO BOTTOM): B. D. FATH; SETH GRANT/WELLCOME TRUST SANGER INSTITUTE

to think and feel. "There are classes of proteins that arrived at different times [in evolution] and expanded at different rates," he says. These expansions, Grant adds, preceded the increase in brain size "as though [they were] a prerequisite for brain size."

For a first pass at revealing the origins of the synapse, Grant's postdoc Richard Emes, now at University College London, looked into the evolutionary history of 650 proteins, all of which operate at the receiving end of the mouse synapse. He sought out the genes for those postsynaptic proteins in 19 species, including tunicates, mosquitoes, nematodes, fruit flies, fish, frogs, cows, dogs, chimps, humans—and even yeast. Even though yeast lacks a nervous system, it uses about 20% of the same proteins employed by the mouse synapse, Grant reported earlier this month at a meeting* in Hinxton, U.K. Only later in evolution, he suggests, were these 120 or so proteins adopted for use in nervous systems.

The insects and nematode had double the yeast's number of mouse synaptic proteins, Grant's team found. All the vertebrates had the full complement of genes for these proteins. Until these results, no one had considered that such big differences in synaptic proteins might exist among species, says Grant.

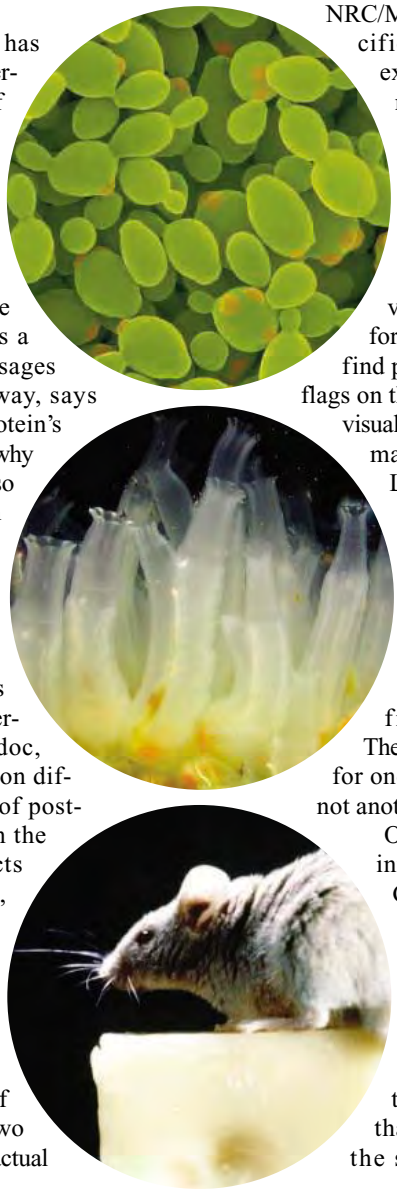
He and his colleagues also examined the species differences in a particularly important set of postsynaptic proteins. This set forms the NRC/MASC complex, a gatekeeper that relays incoming signals and ultimately activates the postsynaptic nerve cell. The "NRC" part has the *N*-methyl-D-aspartate (NMDA) glutamate receptor, which is important in learning and memory, at its core. The "MASC" part centers on the membrane associated guanylate kinase signaling complex.

In vertebrates, the NRC/MASC complex can pack in more than 100 proteins, Emes, Grant, and their colleagues have found. These include neurotransmitter receptors, a calcium ion channel, proteins that connect to signaling proteins inside the cell, kinase enzymes that bind to the calcium channel, and proteins that help hold the whole complex in the right configuration. But in invertebrates, fewer proteins are involved in the complex, Grant reported at the meeting.

This work shows that "the postsynaptic complexes and the [signaling] systems have increased in complexity throughout evolution," says Berit Kerner, a geneticist at the University of California, Los Angeles. In particular, the researchers found that vertebrate NRC/MASC complexes have more receptors and associated proteins, as well as a greater number of enzymes that help set up the signaling pathways. "There's more tools in the toolbox," says Grant.

In addition, his team has discovered a striking difference in the tail of one of the NMDA receptor-associated proteins. In vertebrates, that tail extends through the cell membrane, where it connects to signaling pathways. In invertebrates, the tail is much shorter. As a result, it can't relay messages into the cell the same way, says Grant, adding that the protein's long tail may help explain why the vertebrate synapse is so plastic and can respond in different ways to different incoming signals.

Such evolutionary changes may have also made possible greater diversity within the brains of vertebrates. Chris Anderson, another Grant postdoc, has unearthed brain region differences in the makeup of postsynaptic proteins within the mouse. He tested extracts from 22 brain areas, including the hippocampus, cortex, and cerebellum, for genes and proteins that are involved with the NRC/MASC complex. He also assessed the expression patterns of the genes and labeled two dozen of those proteins in actual tissue samples.



Protein smarts. Synaptic proteins, some of which have their origins in yeast (*top*), increased in number throughout evolution, with mice having more than tunicates (*middle*), possibly explaining ever more complex nervous systems.

The genes for the components of the NRC/MASC complex work in synchrony: When one is active, so are the rest, Anderson reported at the meeting. But to the researchers' surprise, the activity of this collection of genes varied among brain regions. This variation likely enables the different parts of the brain to do their specific jobs, says Grant. Moreover, when the researchers looked at the activity of "ancient" NRC/MASC genes—those also found in yeast and insects—versus the more recent genes found only in vertebrates, they discovered that the recent genes varied most in their expression.

Grant has further observed that eliminating particular proteins in the mouse NRC/MASC complex alters specific cognitive abilities. For example, when one of the recently evolved signaling genes is disabled in mice, causing the rodents to lack a protein called SAP102/Dlg3, the animals have trouble learning spatial tasks but not visual tasks. Typically, mice forced to swim in a tank can find platforms by keying in on flags on the platforms or, lacking a visual cue, by developing mental maps of landing spots. But Lianne Stanford in Grant's lab finds these mice must swim in ever-wider circles to find unflagged platforms. In contrast, mice lacking the gene for another protein in the complex, PSD95, can't find the platforms at all. These genes "can be important for one aspect of cognition but not another," Grant explains.

Other researchers are intrigued by the novelty of Grant's ideas about the evolution of the brain. "They should certainly raise some eyebrows," says Jonathan Flint, a psychiatric geneticist at Oxford University in the U.K. Kerner cautions that other factors, such as the sheer number of cells, likely help explain differences between the invertebrate and vertebrate brain. And Pääbo speculates that invertebrates could have their own undiscovered set of proteins, not present in mammals, that would make their synapses as complex as those in vertebrates. Nonetheless, Pääbo is impressed, noting that Grant "provides a vision for how to approach a perhaps important, unexplored aspect of the evolution of cognitive complexity."

–ELIZABETH PENNISI

* "Integrative Approaches to Brain Complexity" took place 28 September to 1 October in Hinxton, U.K.

CREDITS (TOP TO BOTTOM): DENNIS KUNKEL/VISUALS UNLIMITED; P. DEHAL *ET AL.*, *SCIENCE* **298** (2002); PHOTOS.COM

PUBLIC HEALTH

Gerberding Defends Her Transformation of CDC

The director denies that a reorganization is weakening the public health agency

Hopes were high 4 years ago when Julie Gerberding, a respected infectious-disease researcher, took the helm of the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia. Following the post-9/11 anthrax mail attacks the year before, some in Congress had criticized the nation's premier public health agency for an uncoordinated response. Gerberding, who as CDC acting deputy director for science had emerged as a polished spokesperson for the agency during the crisis, resolved to revamp an organization seen as moving too slowly to address health threats.

She's certainly stirred things up—including some vocal opposition. In 2003 after bringing in management consultants, Gerberding began a reorganization called the Futures Initiative, creating new "coordinating centers" to oversee CDC's existing centers and drawing howls of protest within CDC. The unrest, simmering for years, drew new public attention in September when the *Atlanta Journal-Constitution* ran a lengthy story quoting disgruntled former and current CDC scientists. The article suggested that the turmoil has contributed to the departures of the heads of six of CDC's eight original main centers, such as James Hughes, director of the National Center for Infectious Diseases, as well as other seasoned scientists. The story also revealed that last December, five former CDC directors sent Gerberding a letter expressing "great concern" about "low morale" and "losses of highly qualified and motivated staff."

In press reports, an Internet blog (cdcchatter.net), and conversations with *Science*, CDC staffers have complained that the Futures Initiative has dragged on too long, sapped their time, and added layers of bureaucracy that impede their independence. "There's been a deterioration in our capacity coincident with the deterioration in morale," says Stephen Cochi, a senior researcher in CDC's National Immunization Program. "Something has gone terribly wrong."

Researchers also worry about how Gerberding's still-developing plan to align CDC's budget to match a set of "health protection goals," such as increasing older adults' life spans, will affect research priorities. To her credit, says David Sencer, CDC director from 1966 to 1977 and one of the letter signers, Gerberding has increased efforts to communicate with staff in recent weeks and has announced plans to appoint two ombudsmen: "I think she's trying," Sencer says.

In an hourlong interview last week with *Science*, Gerberding defended her plan to transform CDC and said the mood of many in the agency is upbeat. She pointed to her efforts to branch into new scientific areas such as climate change, expand CDC's extramural grants program, and begin outside peer review of intramural programs. She praised as "extraordinarily gifted" the leaders she's recruited, such as Kevin Fenton, who runs CDC's National Center for HIV, STD, and TB Prevention, and Lonnie King, who directs a new center on zoonotic, vector-borne, and enteric diseases. "There's a difference between our performance in the scientific arena and people's discomfort with some of the things that are going on," Gerberding said, while acknowledging that her radical overhaul of CDC's operations is inevitably prompting "anger" and "grieving."

Below are excerpts from Gerberding's remarks. **–JOCELYN KAISER AND JENNIFER COUZIN**

Q: Whose idea was the reorganization at CDC? Was it your idea?

When the secretary [Health and Human Services Secretary Tommy Thompson] asked me to take the role of CDC, he said, basically, "CDC really needs to modernize." His concern was that times had changed and that CDC was going to have to be a bigger player in the world of preparing for some pretty large-scale health threats.

CDC did not have any goals for the agency. There was really a scientific environment that I find was very strong but not really a broad look at, is the science that we're conducting targeting the health problems of today and tomorrow? What's missing?

We also have to look at the fact that the kind of science that we do is changing. We need to always have gold standard surveillance and epidemiology and the traditional public health sciences, but now we need science in genomics, we need science in climatology with global climate change, we need new science in informatics, and we need new science in health communications. So we have to grow new science at CDC.

Q: Are there areas of research at CDC that you're cutting back on to accommodate some of the expansion?

Not at this time. Our budget is very constrained by very strict budget lines that basically dictate, you spend your money for this.

Q: So you're 3 years into the reorganization. As you know, CDC staff members are saying, "Yeah, we have to change, but let's get it over with." How long do you think this reorganization should take? Has it taken longer than you expected?

Absolutely not. Anybody who's gone through a major organizational transformation knows that you measure the timeline in years.

CREDIT: CDC

Q: We hear from people at CDC saying, "I'm still not sure how my job is going to change." When will they be able to say, "Okay, now I know how my job has changed, and it's not going to really overhaul much more?"

Many of the hard pieces are done. As of October 1st, the management priorities of the year are number one: stability. The main structural reorganizations are approved and in place. It's really time to say, "Let's take a breath, and let's really think about now how do we make the promise that we had when we started this really come true."

Q: Are you concerned that so many senior scientists have left CDC in the last couple of years?

First of all, it's not an unprecedented rate of departures. We have been tracking the attrition rate of scientists, and there's absolutely no change in the trend whatsoever.

Q: What about if you just looked at the number of center directors who left from 1996 to 2001, versus from 2001 to 2006?

I haven't looked over time at the historical attrition of center directors per se. Some of our center directors were no longer in what I would consider to be the most productive phase of their career, and that was something that, you know, is difficult to point out in a public environment. Being a center director is not a life sentence. But we also have some excellent center directors who were recruited to terrific jobs elsewhere, and we were sorry to see them go, believe me. CDC is a good place to recruit from.

We've had a wonderful influx of new, brilliant people who are leading our centers.

Q: In the letter from the former CDC directors, they express concern about how many senior people are leaving and about morale. It seems fairly unusual that five directors would send a letter like that. What do you make of this?

I think [the former directors] weren't conducting a poll of CDC. They were talking to people they respected and they trusted, and they took it very seriously, as I hope I would if I were in their shoes. You know, Dr. [William] Foege [CDC director from 1977 to 1983, a letter signer] was the last person to try to initiate any kind of organizational change at CDC. And when he was going through it, the entire laboratory division of the agency threatened to resign.

We recognize that a change process for a center as large and as successful as CDC is a very difficult undertaking. When you ask people to be more collaborative, or you're asking people to more formally work together for a common goal, it's a new way of working, and not everyone's comfortable with it.

Q: What we've heard is that while that [working together] may be a stated goal, it's not really happening. People feel that because there's additional bureaucracy, it's actually harder to work together.

I think you probably need to talk to more people.

"There are a small number at CDC who are intent on continuing to be critical and are not really willing to say, 'How can we help?' or 'How can we step up to the plate?' "

—Julie Gerberding, CDC

Q: You've said the news reports reflect symptoms of a "disease" at CDC. What do you mean by this?

There are a small number at CDC who are intent on continuing to be critical and are not really willing to say, "How can we help?" or "How can we step up to the plate?" In my opinion, the solution to solving organizational problems is to speak up, not necessarily out.

We're trying to do more to make it safe for people to speak up at every level of the organization, because if we know we've got problems, we can fix them. We're going to try our own blog and really create a system where people can bring their own questions to me anonymously or otherwise, so that we have an informal way of saying, "Gee, how come I can't hire?" or "What is this about performance awards? Let's get the story straight."

Q: Another complaint is that scientists felt, especially early on, that they spent a lot of time on these work groups, and yet in the end, it seems like their advice was ignored.

I completely disagree with that. The people who designed the organizational structure at CDC were scientists [who] came up with three organizational designs, there was lots of conversation about it, and ultimately, you have to pick one. There's no perfect organizational structure in any agency, but we took their advice.

There's a difference between our performance in the scientific arena and people's discomfort with some of the things that are going on. We are performing with excellence, and I cannot find any evidence of any faltering of CDC's performance in the last 3 years. We are the most credible governmental organization if you believe the Harris opinion poll—and we continue to strive to improve even more.

Q: When you look back at your tenure as director so far, are there any mistakes you feel you've made, things you'd do differently in the future, going forward?

I'm kind of a speed-oriented person, and this [the transformation] has taken longer than I wish. But I'm counseled by wise people who have done this kind of thing many times that it always takes years. And I wish that we had been clearer about that expectation at the beginning—that people had been more prepared for the fact that organizational transformation takes a long time, and it's really hard.

Q: How long are you planning to stay [at CDC]? Until the transformation is complete?

I have absolutely no plan to leave right now. [And] I don't think that the transformation will be complete for many years. People who are scientists of organizational design say you check at the 10-year point about your success or failure of the enterprise.

CREDIT: JAMES GATHANY/CDC

PARTICLE PHYSICS

Tidy Triangle Dashes Hopes for Exotic Undiscovered Particles

Physicists have proved that their explanation of matter-antimatter asymmetry is essentially the whole story—even though many hoped the theory wouldn't add up

Most of us would rather be right than wrong, but not so particle physicists. After numerous painstaking measurements—including key observations made earlier this year—they've concluded that their explanation of the subtle differences between matter and antimatter is essentially correct. That marks a major victory for the prevailing theory of particles, the so-called standard model. But it also disappoints researchers who had hoped to find something new to puzzle over.

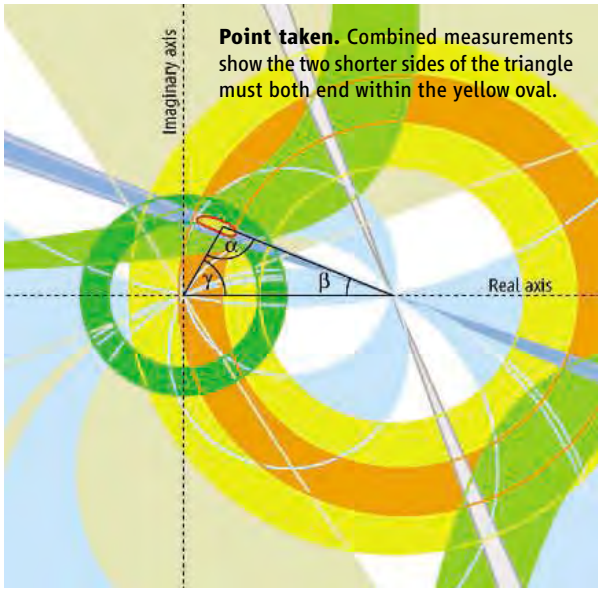
"On one hand, this is a great triumph; all the pieces of the puzzle *do* fit together," says David MacFarlane, a physicist at the Stanford Linear Accelerator Center (SLAC) in Menlo Park, California, and spokesperson for the lab's BaBar experiment. On the other hand, "I would say at least half of us had hoped things would not agree with the predictions of theory."

To test the standard model's explanation of matter-antimatter asymmetry, or "CP violation," physicists performed a dizzying exercise in abstraction. According to theory, the differences can be inscribed in a geometrical construct known as the unitarity triangle. Creating a mosaic of measurements, two teams—the French CKM Fitter group and the Italian UT Fit group—independently confirmed that, to within a small uncertainty, the triangle is in fact a triangle, as they reported this summer.

That shows that the standard model's explanation of CP violation is more or less the whole story, says Stéphane T'Jampens, a CMK Fitter group member at the Annecy-le-Vieux Laboratory for Particle Physics in France. "There is still room for new physics, but not for a dramatic effect," he says.

The fact that the triangle closes means, literally, that the standard model adds up. According to the model, the protons and neutrons in atomic nuclei consist of smaller particles called up quarks and down quarks. These fundamental particles have two sets of short-lived cousins: the heavier charm and strange quarks, and the even-more-massive top and bottom quarks.

One type of quark can transform into another through the "weak interaction," which is how heavier quarks decay into lighter ones. For example, a bottom quark can turn into an up, a charm, or a top, but not into a down or a strange. The standard model catalogs the transformation rates in a grid of numbers called the CKM matrix. If quarks and antiquarks were mirror images, these would be ordinary numbers, particular sums of which would equal 100%. After all, a charm quark must decay into something.



Point taken. Combined measurements show the two shorter sides of the triangle must both end within the yellow oval.

CREDIT: CKM FITTER GROUP

However, as physicists discovered in 1964, matter and antimatter are slightly out of kilter. Theorists can account for this if elements of the CKM matrix are complex numbers: numbers that have an ordinary "real" part and additional "imaginary" part that is multiplied by the square root of negative one. With ordinary numbers in the matrix, the mathematics of the standard model remains exactly the same if particles are swapped for antiparticles and vice versa. Put in complex numbers, and that's no longer true, which means matter and antimatter are no longer symmetric. Some combinations of the complex numbers still add up to 100%. Others add up to zero, and these trace triangles in the plane in which real numbers run across one axis and imaginary numbers run up the other.

In the early 1990s, physicists realized that they might probe the largest triangle by studying particles called B mesons, each of which contains a bottom quark bound to an antiup quark or an antidown quark. (Quarks are never found alone.) In 1999, they completed two "B-factories": the PEP-II collider at SLAC, which feeds the BaBar particle detector, and the KEK-B collider at the Japanese particle physics laboratory KEK in Tsukuba, which feeds the Belle detector.

To determine the angle known as β to high precision, researchers at Belle and BaBar compare the rates at which B^0 (pronounced B-zero) mesons and the antimatter versions of B^0s decay into certain lighter particles. The result defines a narrow blue triangular swath in the plane (see diagram). The teams measure the angles α and γ by studying the decays of B mesons, which define wider gray swaths.

Earlier this year, researchers working with the Tevatron collider at Fermi National Accelerator Laboratory in Batavia, Illinois, helped nail down the length of the right side of the triangle by measuring how fast a B_s (pronounced B-sub-s) meson—which contains a bottom quark and an antistrange quark—transforms into the antimatter version of a B_s in a process known as mixing. That measurement shrank a wide yellow doughnut in the plane to a much skinnier orange one.

These and other swathe and doughnuts overlap in a little region that shows the triangle must come very close to closing. Had the triangle refused to close, that would have suggested that heavy new particles lurk on the high-energy horizon. By quickly popping into and out of existence within a B meson, those particles might have altered the interactions and deformed the triangle.

The triangle may even suggest that new particles will be harder to find at the next great accelerator, the Large Hadron Collider (LHC) currently under construction near Geneva, Switzerland. "There is a suspicion that the fact we're not seeing anything new [in the triangle] suggests that there can't be too many light particles within the reach of the LHC," says Thomas Browder, a physicist at the University of Hawaii, Manoa, and co-spokesperson for the Belle collaboration.

Others are more optimistic about the LHC. And Fabrizio Parodi, a UT Fit member from the University of Genoa in Italy, says that measurements at the B-factories might still show that the triangle is slightly trapezoidal. For now, however, the standard model appears to be on the money. Alas, sometimes a triangle is just a triangle. **–ADRIAN CHO**

EDITED BY YUDHIJIT BHATTACHARJEE

In Print

AVOIDING SEX IN SPACE. Author Laura Woodmansee was ready to sign her new book, *Sex in Space*, at NASA's Jet Propulsion Laboratory (JPL) 22 September. But JPL Ethics Officer Lani De Benedictis and her colleague Bonnie Gerszt had other ideas. They sent an e-mail to thousands at the Pasadena, California, lab shortly before the event, noting that the signing had been canceled "due to ethical issues" that were not specified. Woodmansee complained to JPL officials, and De Benedictis later e-mailed her to explain that the decision was made in part based on the book cover, which shows a not-at-all-racy spiral galaxy behind the provocative title.

Woodmansee says that her book, which quotes NASA scientists, "includes a lot of science about the possibilities of reproduction in space and on other planets." Her previous works include *Women of Space* and *Women Astronauts*. "This has been a heartbreaking week for me," says Woodmansee. "I need to clear my good name as a science journalist, and I'm not sure what to do." JPL spokesperson Veronica McGregor said that the cancellation reflected the lab's policy of not endorsing any products and added that the initial approval to conduct the *Sex in Space* signing was a mistake made by a new employee.

MOVERS

FOCUSING ON SCIENCE. Chemist Chi-Huey Wong admits he will have big shoes to fill when he replaces Yuan-Tseh Lee next week as president of Academia Sinica, which oversees Taiwan's premier research labs. Lee, a chemist and the island's only Nobel laureate, turned Academia Sinica into "a world-class research institution," Wong says. Lee also used his towering authority to influence political elections, steer educational reform efforts, and condemn corruption throughout Taiwan. Wong says he instead intends to focus solely on advancing Academia Sinica's research "to a higher level."

A native Taiwanese, Wong, 58, has spent close to 30 years in the United States. He earned his Ph.D. in chemistry from the Massachusetts Institute of Technology and served on the faculty of Texas A&M University before joining the Scripps Research Institute in San Diego, California, in 1989. Since January 2003, he has also been the director of Academia Sinica's Genomics Research Center. "It's a good time for me to do another type of public service; I'm from Taiwan, so I feel a special responsibility," Wong says.

He believes the key to keeping Academia Sinica on top will be to continue recruiting the best people. But with science budgets rising across Asia, he expects the organization to face stiff competition for talent.

They Said It >>

"I need to show better performance, better books. This will be a rebuilding year."

—Jay M. Cohen, head of the science and technology directorate within the U.S. Department of Homeland Security, after Congress passed the 4-year-old department's 2007 budget on 29 September. Legislators slashed funding for Cohen's Office of University Programs from $62 million to $50 million, citing poor financial management. But they refrained from imposing an anticipated 3-year limit on the funding of university centers (*Science*, 4 August, p. 610).

Awards

PARIS—Mathematician Jacques Stern has been awarded the 2006 Gold Medal of the CNRS, France's basic research agency. Stern, who specializes in computer science and cryptology, says he had no interest in future academic renown but wanted to have an impact on the present world. "At the beginning of my career in mathematical logic, I realized that the results of my work would not be seen for at least a century, if ever. So I looked around for a field where I would see the results quickly," he says. He had been working on mathematical impossibilities; in cryptology, "all I had to do was switch to creating impossibilities for adversaries."

Stern, 57, a professor at the École Normale Supérieure and head of its computer science lab, has broken about a dozen cryptographic systems, including several tough ones offered by major international research groups. He has also developed a mathematical method to prove that a system cannot be attacked and trained about 30 Ph.D.s, including, he says, many "prominent members of the cryptology community." He declines to be drawn out on future plans: "I would like to be surprised and prefer just to wait and see what happens."

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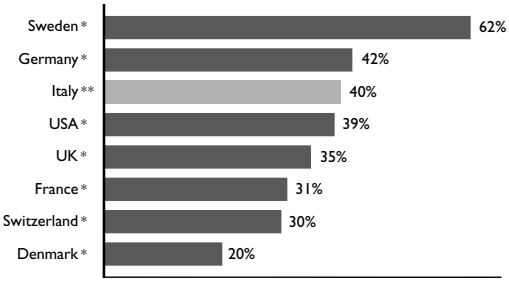
Innovation in Life Sciences Companies: R&D Spending/Revenues *(%)*



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* Critical I "Biotechnology in Europe 2005 Comparative Study"

** Blossom Associati, CrESIT Insubria di Varese University, Italian Biotechnology Report 2006

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Innovation Spotlight

Italy's just launched the first public laboratory for production of personalized anti-cancer drugs for clinical trials

Rome – FaBioCell (Cellular Biological Pharmaceuticals) is the new public laboratory inaugurated by the Italian Minister of Health. Located in the ISS (the Italian National Institute of Health) it will use the dendritic cells of individual patients for the production of anti-cancer drugs and vaccines. It will allow trials of cancer immunotherapy, in collaboration with 3 major Italian hospital centers: Istituto Regina Elena of Rome, Institute for Cancer Research and Treatment (Fondazione G. Pascale of Naples) and the National Cancer Institute of Milan.

Italy to Launch Europe's First Institute for Regenerative Medicine

Modena – The University of Modena and the Eye Bank Foundation of Venice have joined forces to create a public/private partnership forming the Research Center for Regenerative Medicine. It will become the first such center in Europe focused on stem cell therapy for treating vision disorders caused by tissue/organ damage and genetic defects.

The European Institute of Oncology is supported by the US National Cancer Institute for lung cancer research

Milan – The Italy based European Institute of Oncology was selected and funded 850,000 USD by the National Cancer Institute as the best research center in Europe and US to conduct clinical studies for pharmacological prevention related to lung cancer. The research pool is committed to cancer screening with the ultimate and ambitious goal of discovering how to stop lung cancer growth at a very early stage.

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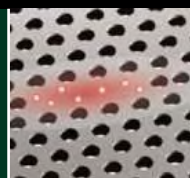

LETTERS | BOOKS | POLICY FORUM | EDUCATION FORUM | PERSPECTIVES

LETTERS

edited by Etta Kavanagh

Cooperating over Water Issues in the Middle East

IT IS THE NATURE OF NATURE IN THE MIDDLE EAST THAT, LIKE EVERYTHING else, all things are political. Even water is laden with politics as raindrops fall either on Jewish or Arab soil. Long before the Israelis described in "Seeking sustainability: Israel's evolving water management strategy" (A. Tal, Special Section: Freshwater Resources, Perspectives, 25 Aug., p. 1081) have a chance to manage water supplies, they must first control the quantity of water that is taken by Palestinians living on the West Bank (*1*–*4*). Within the scientific community, however, there are some contrasts to the military and political conflicts that are so often the fodder for front-page news.

The Alexander River

Three examples of teamwork stand out. The first is the award-winning cleanup of the Alexander River (*5*), which carries raw sewage from the Palestinian towns of Nablus and Tulkarm across the Green Line demarcating the de facto border between Israel and the Palestinian territories on the West Bank. Israeli and Palestinian planners began working together in 1997 and continued through the worst of the Al Aqsa Intifada (2000–05). Implementation of a master plan to restore the river began in 1998 with removal of pollutants, construction of an "emergency project" to treat raw sewage arriving from the Nablus Stream, and creation of seven river parks with bike and pedestrian paths and streamside picnic areas designed in cooperation with Israeli schoolchildren.

The second is a U.S. Agency for International Development–funded Israeli/Palestinian research project to assess damage and prepare for eventual restoration of water in the Besor/Khalil watershed. The Besor/Khalil's headwaters rise in the West Bank, where it collects the raw sewage of Hebron and the Jewish settlement of Kiryat Arba before running into Israeli territory. It flows through the northern Negev Desert, gathering yet more sewage, storm water, and agricultural and industrial waste, before becoming the only flowing surface water stream in the Gaza Strip (see also "Running out of water—and time," J. Bohannon, 25 Aug., p. 1085). Israeli Jewish, Israeli Arab, and Palestinian scientists are preparing a joint quantitative analysis of water quality and watershed impairment from the river's source in the West Bank highlands to its outlet in the Mediterranean (*6*).

Finally, in a project called Good Water Neighbors spearheaded by Friends of the Earth Middle East, Israelis, Palestinians, and Jordanians are cooperating to share best practices for water conservation. The cooperation of 17 cross-border communities has illustrated how the interdependent nature of water can create the initial trust that provides the basis for cooperative work (*7*). For example, Palestinian, Jordanian, and Israeli mayors have jointly called for policies to rehabilitate the lower Jordan River.

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What Happens to the Whistleblowers?

I AM TROUBLED BY THE COMMENT OF IRWIN Goldman in the article "Truth and consequences" (J. Couzin, News Focus, 1 Sept., p. 1222). The article states that Goldman "came to believe strongly that science needs individuals like [the student whistleblowers at the University of Wisconsin (UW)]." Yet most of the students involved scattered, leaving UW, leaving graduate school, leaving academia, even leaving science. I feel that Goldman and others showed commendable support for these students during the ordeal they suffered, but once it was over, the students were left high and dry. No wonder they left. The article mentions Goldman's plan for a policy to protect students in similar situations, but again, the policy he envisions seems designed to protect students during the investigation and makes no provisions for the aftermath. I agree that we cannot change our standards of what a Ph.D. means, even for a student who has studied for years in a lab that is suddenly discredited. She obviously cannot receive a degree until she has completed and defended a dissertation. And yet, surely some accommodation can be arranged for people in this situation. Did UW

CREDIT: SHAI GINOTT/CORBIS

do everything in its power to find labs for these students? Or were they all too happy to see the last of them? I wonder if government funding agencies (e.g., NIH) are considering provisions for NIH-funded students and postdocs caught in such a situation.

RACHEL L. RUHLEN

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A Problem with Mentoring

I READ THE ARTICLE "TRUTH AND CONSEquences" (J. Couzin, News Focus, 1 Sept., p. 1222) with dismay, not all of it directed at the obvious scientific misconduct. The University of Wisconsin (UW) let these six students down well before the misconduct was discovered. As a student at UW, I earned an M.S. and Ph.D. and published two papers in 4 years. Some of these students had been in the lab 6 to 7 years and had published nothing. Didn't anyone notice they weren't making progress? Didn't they have committees reviewing their work? Now I have the opportunity to mentor students and postdocs. Students not making progress because they lack the skills or commitment, or have extenuating circumstances in their lives are usually easy to identify. If a student doesn't fit that category, then the mentor deserves scrutiny. Universities have an obligation to do this. (They might also consider some mentor training.) As a parent observing my children and their colleagues in graduate schools, lack of regard for the student's time investment is not unique to UW. Universities should design their Ph.D. programs to be accomplished in 4 to 5 years, and while scrutinizing their programs, they might ask if the training they provide is suitable for the available opportunities. Subtract the number of faculty a department hires from the number of Ph.D.s they produce, and it's apparent that students need to be trained for more than university careers. If we misuse our young people, we are bankrupting the future of science, not only by losing potential talent but by alienating the public we expect to support science in the future. UW (and others)

Letters to the Editor

Letters (~300 words) discuss material published in *Science* in the previous 6 months or issues of general interest. They can be submitted through the Web (www.submit2science.org) or by regular mail (1200 New York Ave., NW, Washington, DC 20005, USA). Letters are not acknowledged upon receipt, nor are authors generally consulted before publication. Whether published in full or in part, letters are subject to editing for clarity and space.

needs to take steps to ensure that the mentoring of graduate students is adequate and also should have the grace to say "I'm sorry" to the students who wasted years because of bad mentoring.

MARYJANE SELGRADE

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Mice, Pain, and Empathy

IN THEIR REPORT "SOCIAL MODULATION OF pain as evidence for empathy in mice" (30 June, p. 1967), D. J. Langford *et al.* seek to test the hypothesis that mice can empathize. I found myself filled with empathy for the subjects of the experiments. Research that describes intentionally induced "writhing and pain" needs to have better ends than knowing if mice might feel empathy for each other. I have always defended the use of animals in scientific research, but only on the condition that they do not suffer pain, at least no more than we would be prepared to inflict on ourselves in the pursuit of science. There are so many experiments that might satisfy our curiosity, but we cannot seriously study empathy with such a clear disregard for it ourselves. We have to find other ways to discover what is going on in the minds of animals that can feel pain. Perhaps the experimenters could consider using signs of pleasure and relaxation following some reward to see if this behavior transfers some signal. I acknowledge that this cannot be an alternative to empathizing with those in pain, but it is at least a painless parallel. But there must always be research that we will not do. Your report by Greg Miller on this research in the News of the Week section ("Signs of empathy seen in mice," 30 June, p. 1860) starts, "Empathy is one of the nobler human attributes." Must I conclude that it is absent or suppressed in some scientists?

ERNEST GWYN JORDAN

Benfleet, UK.

Response

I AGREE THAT WE AND OTHER SCIENTISTS HAVE serious ethical obligations in relation to research that involves inflicting pain on animals: the goal of the research must be important, it cannot be realized without inflicting pain, and the least pain possible is inflicted.

As to our goal, I would remind Jordan of the disturbingly high prevalence of chronic pain (up to 50% of the general population) (*1*), and our continued inability to adequately manage chronic pain in many sufferers. It is well known that social factors can robustly modulate chronic pain in humans (*2*, *3*), but without any animal models, the mechanisms by which they do so remain obscure.

As to the means, the offense appears to be our use of the "writhing test," developed in 1959 (*4*). This very common, but unfortunately named, assay involves the intraperitoneal injection of very dilute acetic acid, which inflames the viscera and muscle wall. The stereotypical, reflexive constrictions of the abdominal musculature produced have historically been termed "writhes," but "stretches" would be a more accurate description, since there is virtually no motion perpendicular to the long body axis. The writhing test is likely the least intense pain model in current use, in that the behavior can be totally abolished by low doses of opioids and moderate doses of over-the-counter analgesics (*5*). The mouse formalin test also responds to weak analgesics. In fact, rather similar assays are indeed performed on human volunteers, involving, for example, the injection of hypertonic saline into the cheek (*6*). Ironically, we chose the writhing test precisely because it is of the mildest intensity available, to improve our ability to see the subtle changes produced by social factors. Thus, what is implied by the phrase "writhing in pain" really does not apply in our experiments.

As to alternatives not involving pain, the possibility that we might study empathy using reward and "signs of pleasure and relaxation" begs the availability of valid dependent measures of these states in mice. In any case, our original purpose was not to provide evidence of mouse empathy, but rather to study the social modulation of pain itself. If in fact we have succeeded, serendipitously, in developing a mouse model of empathy, then the full power of mouse genetics can now be applied to elucidating not only the neurobiological mechanisms underlying social modulation of pain in humans but also mechanisms underlying psychopathy and autism, disorders featuring impaired ability to empathize.

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CORRECTIONS AND CLARIFICATIONS

Reports: "Washing away your sins: threatened morality and physical cleansing" by C.-B. Zhong and K. Liljenquist (8 Sept., p. 1451). In Table 1, the Study 3 data were entered incorrectly. The percentage who chose antiseptic wipes in the ethical recall condition was 37.5%, not 33.3%, and the percentage who chose antiseptic wipes in the unethical recall condition was 75%, not 66.7%.

ScienceScope: "New Vatican astronomer" by C. Holden (25 Aug., p. 1031). The article incorrectly reported that George Coyne had been fired from his position; in fact, the astronomer had asked to be replaced after 28 years as director of the Vatican Observatory. He will remain as president of the observatory's foundation.

Reports: "Measurement of forces inside a three-dimensional pile of frictionless droplets" by J. Zhou *et al.* (16 June, p. 1631). Although reference (*24*) was cited in the context of the theoretical aspects of the paper, the authors wish to note that the group of Brujic, Edwards, Makse, *et al.* also used microscopy of droplet contacts to measure the distribution of forces within a three-dimensional sample. See also J. Brujic, S. F. Edwards, D. V. Grinev, I. Hopkinson, D. Brujic, H. A. Makse, *Faraday Discuss.* **123**, 207 (2003).

Reports: "Complete photo-induced breakup of the H_2 molecule as a probe of molecular electron correlation" by W. Vanroose *et al.* (16 Dec. 2005, p. 1787). In Fig. 2, molecules were drawn in the wrong orientation. In Fig. 3D, the image was misplotted. The correct figures appear here.

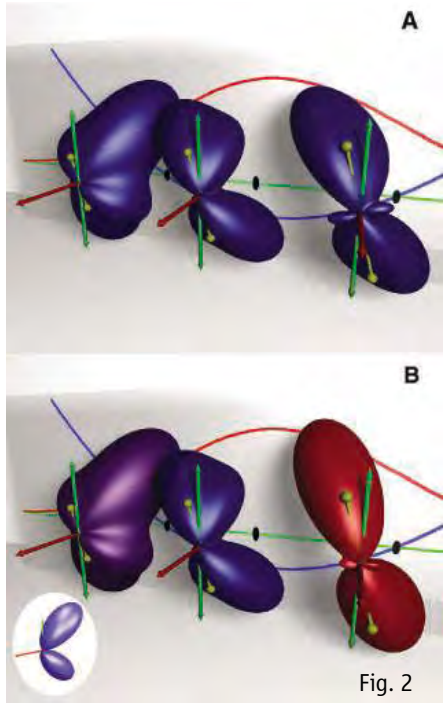

Fig. 2

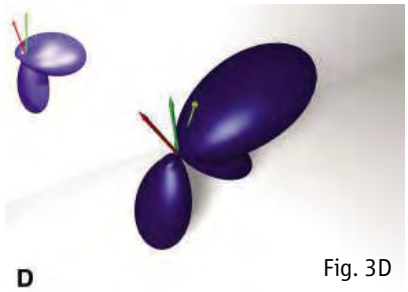

Fig. 3D

PLANETARY SCIENCE

How to Build Planets

Caleb A. Scharf

Few questions are as ancient and compelling as that of how the world beneath our feet originated. Countless societies have sought an answer, developing varied and intriguing cosmographies that, however, often reveal more about their authors than the origins of Earth. In 1644, Descartes made what can be considered the first steps toward a reasoned description of planetary origins. His view, philosophical in nature, theorized that Earth and the other planets surrounding the Sun originated from a system of vortices. About a hundred years later, Kant and Laplace formulated what would become an underlying principle of modern ideas regarding the origin of the solar system. Their nebular hypothesis suggests that Earth and the other planets formed contemporaneously with the Sun from a cloud of gas that collapsed due to gravity into a rotating, flattened disk of material. This picture appears to be correct. In the past decade, almost 200 planetary systems beyond our own have been discovered, along with a multitude of embryonic, protoplanetary systems. We now have the means not only to investigate the universal origins of worlds but also to hold our own up in comparison to others. This is a tremendously exciting time, reinvigorating many classical scientific disciplines, often in unprecedented collaboration.

Planet Formation
Theory, Observations, and Experiments

Hubert Klahr and Wolfgang Brandner, Eds.

Cambridge University Press, Cambridge, 2006. 318 pp. $120, £65. ISBN 0-521-86015-6. Cambridge Astrobiology.

The multidisciplinary nature of this subject is evident in the 17 review papers written for *Planet Formation: Theory, Observations, and Experiments*. This carefully organized text, edited by Hubert Klahr and Wolfgang Brandner (Max-Planck Institute for Astronomy) represents a snapshot of the state of the art of the modern quest for the origins of worlds. Rather than developing contributions in isolation, this volume is based directly on the discussions and presentations of astronomers, planetary scientists, and meteoriticists during a snowbound December 2004 meeting in a Bavarian castle. One suspects that a rather good time was had by all.

Reading through the volume, one learns that protoplanetary systems (both observed and hypothesized) can be enormously complex. It naturally follows that formed planetary systems must have considerably diverse properties. No single world is likely to have an exact duplicate, either among its immediate siblings or within the myriad systems in our galaxy. Gas, microscopic dust, ices, and rocky planetesimals are drastically processed and often reprocessed en route to becoming planets. These raw ingredients drift and circulate as the protoplanetary disk and the central protostar evolve. Their cooking takes many forms, from the coagulation and fragmentation of solids to the accretion or photodissociation of gases. It also involves widely varying thermal and radiation environments as well as a perplexing array of possible chemical pathways.

Despite this complexity, research is revealing common mechanisms. Disentangling the factors that determine orbital architecture and the formation of major planets arguably remains the most urgent problem, but more subtle phenomena must also be tackled. These raise fascinating questions about the composition of materials in planetary systems and the asteroidal and cometary detritus littering them. It is probably no overstatement to say that such details ultimately relate to the origins of life itself.

The logical arrangement of chapters and consistent cross-referencing by the authors and editors will help readers navigate the interconnections among these complex phenomena and, more broadly, between the fields of planetary science and astronomy. This is a collection aimed squarely at a highly informed, technical audience. Nonetheless, a sense of excitement and scientific novelty persists in the many detailed passages.

The historical context of planets and their origins is used to set the stage for our new perspective on protoplanetary disks. Experimental work on the collision and coagulation of dust grains follows from the latest work in meteoritics and leads into observational and theoretical research on the mechanics of protoplanetary disks and planet formation. Some of the pictures the contributors paint are quite evocative: The forming rocky embryos of giant planets hustle and bustle the material of the surrounding disk, sometimes forcing smaller objects to their doom in the young star, sometimes acting like good shepherds and halting their infall. A delicate chronological ballet takes place between the protoplanetary disk shedding its gaseous material to interstellar space and the need of forming worlds to gather up matter. Further afield, there are tricky, and fascinating, questions about brown dwarfs—objects straddling the regime between what we are familiar with as stars and planets. Are they failed stars or greedily bloated planets? Bonding the various topics together are the meticulous astronomical techniques of planet and disk detection, rooted in astronomical history but ultramodern in application.

Waiting for work. Arthur Dent visits the planet designer Slartibartfast (left), in the 1981 BBC Television series *Hitch-Hiker's Guide to the Galaxy*, by Douglas Adams.

The origin of planetary systems is a compelling subject rejuvenated by recent discoveries and one that deserves a thorough technical reference work. A distillation of such a rapidly evolving scientific field comes with some risk. New discoveries will inevitably overtake the wisdom contained therein. Both depth and generality are therefore required. *Planet Formation* applies solid workmanship to the task, providing a definitive text for the shelves of researchers, students, and interested bystanders that should prove to be of considerable longevity. Even

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Slartibartfast and Douglas Adams, to whom this volume is dedicated, might find it handy.

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ECOLOGY

Fighting Fire with Common Sense

Ted Steinberg

Look out, Smokey the Bear, there's a contract out on your life. Some of the authors represented in *Wildfire: A Century of Failed Forest Policy* want you dead.

Smokey the Bear was invented by the U.S. Forest Service in 1944 as part of the campaign to fight forest fires. That war on fire began with the Great Fires of 1910, which burned millions of acres in the American West. There was a brief respite in this century-old conflict during the 1970s and 1980s, when the Forest Service allowed fires caused by lightning strikes to burn without immediately calling in the crews. But this lull in the fighting ended with the 1988 Yellowstone Park fires, which scorched over two million acres. Since 1988, the Forest Service, with time on its hands because it is now less involved in supervising logging operations, has rarely seen a wildfire it did not douse. The authors of the essays in this collection—published by the Foundation for Deep Ecology, an environmental advocacy group founded by former clothing magnate Douglas Tompkins and wedded to less anthropocentric approaches to nature—want to end this war and the "fire-industrial complex" that underwrites it.

Wildfire
A Century of Failed Forest Policy
George Wuerthner, Ed.
Foundation for Deep Ecology, Sausalito, CA, in association with Island Press, Washington, DC, 2006. 352 pp. $75. ISBN 1-59726-069-X. Paper, $45. ISBN 1-59726-070-3.

The history of fighting fires, the authors argue convincingly, has been self-defeating and based on unscientific assumptions about the role of fire in the continent's ecology. They point to evidence that fire is a long-standing phenomenon and that the landscape of the American West especially has evolved in conjunction with it. A 2000 study, for example, based on charcoal and pollen analysis, revealed that the 17,000-year history of Yellowstone Park has been punctuated by periodic large blazes. The 1988 fires, in other words, were hardly anomalous.

Far from being the negative, disastrous force it is often made out to be in media reports, wildfire serves a range of positive ecological functions. These blazes can kill pathogens, aid in the soil-building process, and increase soil fertility. The snags left in the wake of wildfires, meanwhile, create valuable habitat for birds and mammals.

Moreover, with 622 million acres of public and private grassland and forest at risk—ranging from moderate to high—of catastrophic conflagration, the federal government simply cannot afford to win this millennial battle with nature.

But that fact has not stopped the Bush Administration from pushing through Congress the Healthy Forest Restoration Act of 2003. Recruiting the 2002 Biscuit Fire in Oregon to his cause, President Bush argued that the timber industry needed to be allowed to thin trees from the forest in order to prevent similar forest fires in the future. Yet as the authors of this volume point out, the legislation has simply allowed loggers to cut the larger trees, precisely the trees that are least susceptible to fire. The legislation, writes George Wuerthner, "will undoubtedly increase the health of bank accounts for commercial logging and livestock grazers but will do less toward promoting real ecological health on the nation's public lands."

If the war on fire is a scientifically bankrupt one and President Bush is simply trying to extend it to the profit of commercial interests, what then is the right approach to fire? Turning the land "back to nature" is one proposal that surfaces repeatedly in this volume, although one wonders exactly what that would mean. Even if every American could recite by memory Gary Snyder's Buddhist "Smokey the Bear Sutra" (which concludes the volume) with its plea for "harmony of man and nature" (*1*), it is hard to see how that would change the way the Forest Service and timber and grazing industries do business.

Critical ecological force. Fire in Yellowstone National Park, 1988.

CREDIT: GEORGE WUERTHNER

Equally convincing, perhaps, are the photographs on display in this volume. The beautiful and arresting images of Western landscapes in the wake of fire will leave most readers hard pressed to envision fire as simply a destructive force. Still more convincing are the calls by economist Thomas Michael Power for better building codes in wildland areas and hazard zoning to keep people and property out of harm's way. The laissez-faire approach that has tended to govern land development in the United States in the period since World War II is in need of the kind of reform that has happened in Summit County, Colorado. People there are required to use fire-resistant materials and prune trees when building in forested areas. Even simply keeping the roofs and gutters free of flammable debris will help because only rarely is the heat from a forest fire alone enough to cause a house to erupt in flames.

In his contribution to the volume, Andy Kerr suggests that rather than introducing the kids to Smokey the Bear, we ought to be telling them about Reddy Squirrel, a creation of the Forest Service Employees for Environmental Ethics. Reddy wants homeowners to learn that wildfire is a fact of life in the woods and that rather than wait for the smokejumpers to arrive they are better off removing brush from their yards and making sure their homes have tile roofs, not shake shingle ones. It is time for Smokey to retire anyway; most people know not to play with matches. Better that they learn this little squirrel's motto: "Forest Fires Happen. Be Ready."

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10.1126/science.1133695

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ECOLOGY

Millennium Ecosystem Assessment: Research Needs

The research community needs to develop analytical tools for projecting future trends and evaluating the success of interventions as well as indicators to monitor biological, physical, and social changes.

Stephen R. Carpenter,[1] Ruth DeFries,[2] Thomas Dietz,[3] Harold A. Mooney,[4]† Stephen Polasky,[5] Walter V. Reid,[6]* Robert J. Scholes[7]

The Millennium Ecosystem Assessment (MA) was designed to meet the needs of decision-makers for scientific information on the consequences of ecosystem change for human well-being (*1*–*3*). Even though the intended audience is decision-makers, the scientific community is involved as assessments are being made, especially when research and data gaps become apparent. Here we summarize the most important information needs encountered in the MA work.

Enhanced online at www.sciencemag.org/cgi/content/full/314/5797/257

Basic Theory

We lack a robust theoretical basis for linking ecological diversity to ecosystem dynamics and, in turn, to ecosystem services underlying human well-being. We all need this information to understand the limits and consequences of biodiversity loss and the actions needed to maintain or restore ecosystem functions.

The most catastrophic changes in ecosystem services identified in the MA involved nonlinear or abrupt shifts. We lack the ability to predict thresholds for such changes, whether or not a change may be reversible, and how individuals and societies will respond. Thus, the risks of ecosystem catastrophes are poorly quantified. Major ecosystem degradation tends to occur as syndromes of simultaneous failure in multiple services. For example, the populous dry lands of the world are facing a combination of failing crops and grazing, declining quality and quantity of fresh water, and loss of tree cover. Similarly, many rivers and lakes have experienced increases in nutrient pollution (eutrophication), toxicity, and biodiversity loss.

Relations between ecosystem services and human well-being are poorly understood. One gap relates to the consequences of changes in ecosystem services for poverty reduction. The poor are most dependent on ecosystem services and vulnerable to their degradation. Empirical studies are needed.

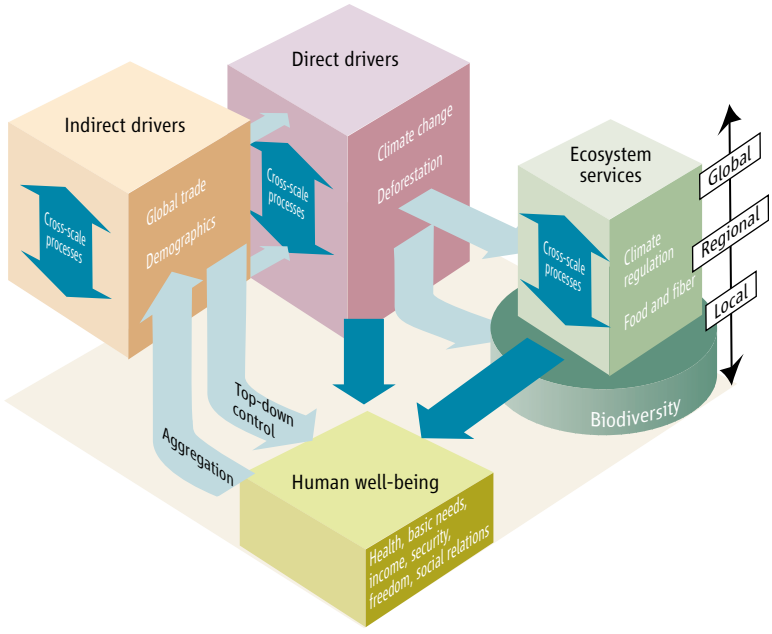
Local to Global Scales

Local processes sometimes spread to become important regionally or globally, but ecosystem services at more aggregated scales are seldom simple summations of the services at finer scales. An example of a cross-scale effect is the loss of buffering coastal ecosystems that exposed extensive regions to catastrophic damage in the 2004 Asian tsunami and the 2005 Gulf of Mexico hurricanes. Conversely, most services are delivered at the local scale, but their supply is influenced by regional or global-scale processes (see figure). Although there are many case studies, our capability of predicting emergence of cross-scale effects and their impacts on ecosystem services is limited. A related problem is the mismatch between the scales at which natural and human systems organize. These lead to failures in feedback, when, for instance, benefits accrue at one scale, but costs are carried at another. We need robust, manageable frameworks for analyzing ecosystem services at multiple scales. Inclusion of "subglobal" assessments in the MA was a tentative step in this direction.

Monitoring and Indicators

Despite advances in monitoring technology, the lack of uninterrupted time series of sufficient length to reflect social-ecological dynamics is a major problem. More disturbingly, the information available today is sometimes of poorer quality than historical information. For example, hydrology monitoring networks in many countries are deteriorating, and institutions to maintain long-term records of Earth observations from satellites are not in place.

Specific data gaps that posed serious constraints in the MA analysis include the lack of (i) global time-series information on land cover change; (ii) adequate information on location and rate of desertification; (iii) global maps of wetlands distribution; (iv) systematic information



The MA conceptual framework (*2*), modified to illustrate connections among local, regional, and global scales for a few processes. Light blue arrows indicate actions that are amenable to policy interventions.

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on stocks, flows, and economic values of many ecosystem services (e.g., freshwater fisheries, natural hazard regulation, groundwater, and pollination); (v) knowledge of trends in human reliance on ecosystem services, particularly services without market values (e.g., domestic fuel wood and fodder); (vi) systematic local and regional assessments of the value of ecosystem services; and (vii) connections between data on human systems and ecosystems. Trends in ecosystem services are often most effectively communicated through indicators that simplify and synthesize the underlying complexity (*4*). Many ecosystem indicators have been proposed [e.g. (*4*, *5*)], but there is no consensus on a manageably small set that can be consistently applied and serves the needs of decision-makers and researchers.

There are challenges to developing indicators of ecosystem services. How can observable attributes of ecosystems and human well-being be linked? How can indicators be aggregated across spatial scales without smoothing out important heterogeneity? How can indicators reflect future consequences for human well-being? What is the minimal set of indicators to represent multiple facets of ecosystem services? Assessments must convey the confidence attached to particular indicators. In most cases, the MA was unable to quantify uncertainty. Work is needed to improve identification, quantification, and communication of uncertainties (*6*–*9*).

Attributes used for monitoring social and economic variables, such as gross domestic product or population, have been collected over long periods and have an established role in decision-making, but their spatial resolution is coarse. Biophysical observations typically have great spatial detail, but short records and little political traction. Integrating both types of data into policy discussions is a key challenge.

Policy Assessment

Existing policies constitute "experiments" from which we can learn (*10*). For example, there has been a proliferation of biodiversity conservation strategies designed to increase local incentives for conservation. Yet, McNeely *et al*. (*11*) conclude that "A key constraint in identifying what works and what does not work to create economic incentives for ecosystem conservation is the lack of empirical data supporting or refuting the success of *any* approach." We already have evidence that sustained interdisciplinary effort can yield sound science and practical guidance (*12*).

We need to understand how the effects of response strategies vary among ecological and social contexts. We don't know what conditions must be met or how to tailor planning and decision-making to local circumstances. Even in the few cases where research has explored options to maximize individual services (such as crop production), there is limited research into trade-offs with other ecosystem services (such as water resources or biodiversity). Understanding of the costs and benefits of alternative management approaches for the entire range of ecosystem services is essential. The few examples that assess the bundle of ecosystem services provided by a region show that a single-service analysis misses key trade-offs (*13*).

Linking Social to Ecosystem Change

Most research related to ecosystem services focuses on direct drivers, such as land use change or invasive species. Yet, effective management requires more attention to indirect drivers such as demographic, economic, sociopolitical, and cultural factors. In their assessment of forest responses, Sizer *et al*. (*14*) conclude that "[Forest sector] outcomes tend to be shaped as much or more by policies and institutions related to trade, macroeconomics, agriculture, infrastructure, energy, mining, and a range of other 'sectors' than by processes and instruments within the forest sector itself." In some cases, indirect drivers may provide better leverage points for policy than the direct drivers (*15*).

People have enormous capacity to adapt. Thus, investments in education and technology have substantial implications for future ecosystem services. However, we have limited capacity to project the effects on ecosystem services of investments in education or development of green technology.

Economic Instruments and Valuation

The MA found potential in economic incentives to improve ecosystem management, but little research on the effectiveness of different approaches. At present, most ecosystem services are not marketed. The resulting lack of information about prices that reflect social value is an impediment to design and implementation of economic policy instruments. The gap is particularly acute for "regulating services," such as disease and flood regulation and climate control, which are rarely priced, yet have strong effects.

Valuation translates ecosystem services into terms that decision-makers and the general public can readily understand (*16*). The MA attempted to provide a systematic accounting of the value of changes in ecosystem services but was limited in its ability to do so. Often, the ecological production functions that describe the relation between ecosystem condition and the provision of ecosystem services have not been quantified. Too often, ecological and economic studies are carried out separately; as a result, the most reliable ecological and economic information cannot be brought together.

Conclusions

Meeting the research needs described will require new coalitions among disciplines that traditionally have been isolated and funded by programs that are discipline-specific. It also requires much greater interaction among resource-based institutions and their policy processes. Achieving a sustainable world depends on a full understanding of the connections between ecosystems and human well-being and the drivers and responders to change. The MA has provided a road map; now, we need to start the journey.

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GENETICS

The Bacterial World Gets Smaller

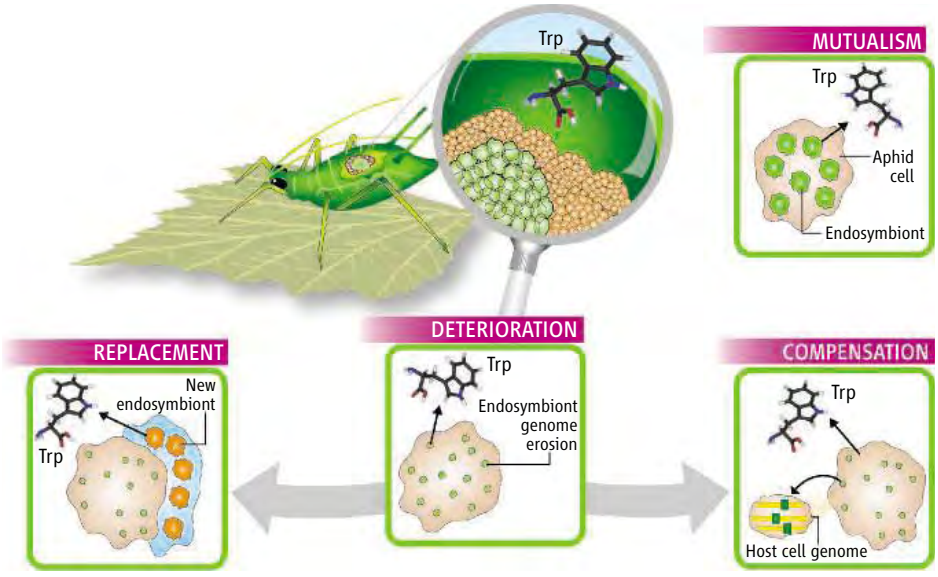
Bacterial symbionts with miniscule genomes can survive by relying on gene expression by host cells or other symbionts. This system may mimic the process of organelle genome evolution.

Siv G. E. Andersson

The race to find the smallest microbial genome has taken an amazing turn. On page 312 of this issue, Pérez-Brocal *et al*. (*1*) report the ~422-kb genome of an aphid endosymbiont, *Buchnera aphidicola*. Even smaller is the ~160-kb genome of a psyllid endosymbiont, *Carsonella ruddii*, reported by Nakabachi *et al.* on page 267 (*2*). These two bacterial genomes are the smallest sequenced to date. In addition to satisfying our desire to crown world-record holders, the genomes tickle our curiosity by approaching the sizes of terrestrial plant mitochondrial (<600 kb) and chloroplast (<220 kb) genomes.

Symbiotic relationships are widespread among invertebrates, including medically and agriculturally important pests. An estimated 10% of insect species house "farms" of bacterial endosymbionts that provide nutrients such as cofactors, amino acids, or other essential compounds that the host insects cannot obtain from their diet (*3*). The best-studied example is *B. aphidicola*. This bacterium, which produces all the essential amino acids except tryptophan, resides within a specialized group of aphid cells (see the figure). *B. aphidicola* has been directly inherited from insect mother to offspring for a few hundred million years. During the evolution of this host-symbiont relationship, approximately 75% of the ancestral *B. aphidicola* genome has been eliminated, resulting in genomes that are currently 600 to 700 kb in size (*4*–*6*). This small genome size is indicative of a closed ecosystem in which a bacterial genome encodes the near-minimal set of genes required for bacterial growth (*7*). Indeed, ~88% of the endosymbiont enzymes can be predicted by computer network analysis of minimal reaction sets stimulated under endosymbiont growth conditions (*8*).

Not only are these two bacterial genomes among the smallest, they are also among the most stable, with no acquisition of external DNA, no repeated sequences greater than 25 bp, and no chromosome rearrangements over the past 50 to 100 million years (*5*). This would represent a biological system of heavenly bliss, were it not for the slow erosion of endosymbiont genomes. This deterioration accounts for an estimated loss of about one gene per 5 to 10 million years (*5*). This is as expected from Muller's ratchet (*9*), which proposes that deleterious mutations accumulate in small asexual populations with no incorporation of new genes. In effect, such organisms may decrease in fitness over time until they become extinct. It is debated whether sequence erosion will eventually come to a halt, or whether endosymbiont genomes will continue to deteriorate, causing the demise of these microbes and the collapse of their hosts.



Endosymbiont evolution. Many insects contain bacterial endosymbionts (green) that produce essential compounds, such as tryptophan (Trp), for the host (mutualism). As the endosymbiont's genome diminishes (deterioration), lost gene functions can be rescued (replacement) by the gain of a secondary endosymbiont (orange). Alternatively, endosymbiont genes can be transferred to the host nuclear genome (compensation).

The two genomes presented in this issue have surpassed the previous lower limit for sequenced genomes of *B. aphidicola*, which range in size from 615 to 641 kb. The genome of *B. aphidicola* from the aphid *Cinara cedri* (the *B. aphidicola* strain BCc) consists of a ~416-kb chromosome with 362 protein-coding genes and a 6-kb circular plasmid (*1*). The ~160-kb chromosome of *C. ruddii* encodes no more than 182 proteins (*2*). Absent from both organisms are genes encoding most membrane and transport functions, a finding indicative of freely diffusible systems with a passive exchange of metabolites. Surprisingly, no genes for the biosynthesis of tryptophan were identified in the BCc genome, although it has been shown experimentally that the aphid host is dependent on the bacterial provision of tryptophan (*10*). Intuitively, we would expect such extensive gene loss in an endosymbiont genome to be lethal for the insect.

Pérez-Brocal *et al.* suggest a possible way out of this conundrum—replacement of the BCc strain with a secondary endosymbiont to supply tryptophan. Indeed, it has been shown experimentally that it is possible to force secondary symbionts to take over the functions of primary endosymbionts if infected into aphids that have been cured of their primary endosymbionts (*11*). This offers a solution to the dreaded "collapse" scenario; although the ancestral endosymbiont may become extinct, the aphid population will be saved by fresh endosymbionts that gradually replace the deteriorating ones. This is consistent with mathematical modeling, which predicts that strong host-level selection will usually protect the endosymbiont genomes from extinction, but that deleterious mutations will rapidly proceed through the process of Muller's ratchet if host fitness is preserved by compensatory changes elsewhere (*12*).

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Nakabachi *et al.* suggest a different scenario to explain the loss of genes in the *C. ruddii* genome—the transfer of endosymbiont genes to the host nuclear genome for expression. Parallels can be drawn to organelles such as mitochondria in that most genes encoding mitochondrial proteins are located in the cell's nuclear genome. Some of the genes may have been transferred from an ancestral endosymbiont, whereas others represent modified cytosolic cellular proteins recruited for service in the mitochondrion (*13*). Deterioration and gene loss are evident in both organelle and endosymbiont genomes despite strong host-level selection. This is because the balance between the two opposing forces—deleterious mutations and host-level selection—shifts toward mutational erosion when the destroyed functions are compensated by genes from other endosymbionts or by a cell's nuclear genes.

The endosymbionts of insects are an excellent model system to test theoretical predictions about the evolution of genome size in small, nonrecombining bacterial populations. As we continue to study these systems, we are likely to discover even more extreme examples of miniscule bacterial genomes. A stronger focus is needed on the compensatory changes that have taken place in the secondary endosymbionts and the nuclear genomes of the hosts. The results will provide hints about the processes shaping the development of organelles and the various routes taken to minimal gene-sets in nature. Potential applications include new weapons in the fight to eliminate agricultural pests and vector-borne diseases. However, for the smallest of small endosymbionts (*1*, *2*), the future seems gloomy. It is a dead end from which there is no escape.

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APPLIED PHYSICS

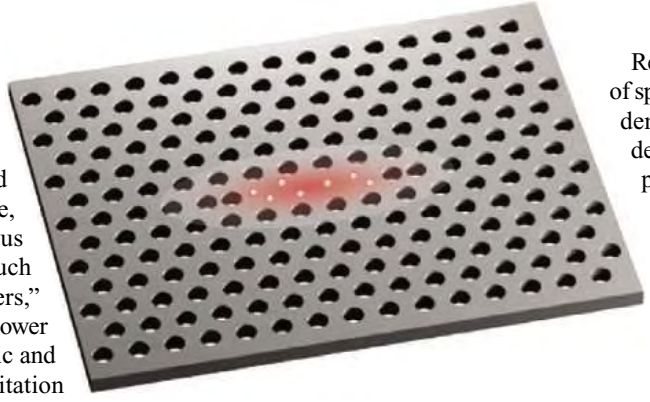
Seeking the Ultimate Nanolaser

Combining photonic nanostructures with quantum dots may lead to semiconductor lasers having much higher efficiency and performance.

Susumu Noda

Semiconductor lasers generally emit a large amount of undesired spontaneous emission before starting lasing oscillation, which degrades their efficiency and performance substantially. Therefore, lasers that emit almost no spontaneous emission have long been sought. Such devices are called "thresholdless lasers," where light output versus excitation power has no obvious threshold characteristic and lasing occurs at extremely low excitation powers. These lasers should have the maximum allowable performance and thus be very useful for optical applications. One promising approach has been to construct lasers with a nanocavity in a photonic crystal, in which the optical properties are structurally designed rather than intrinsic to the material. The photonic crystals and nanocavities can then be tailored to control spontaneous emission to achieve thresholdless operation. Recent progress in the engineering of photonic crystal nanocavities and their combination with quantum dots has accelerated this effort (*1*–*4*).

Several key issues (*5*) must be addressed before thresholdless lasers can be realized. The threshold behavior of semiconductor lasers arises from spontaneous emission coupled to the many optical modes inherent to the laser cavity. Only one of these can be the lasing mode. The undesired spontaneous emission into other modes dissipates the excited carriers in the semiconductor and, consequently, the laser efficiency is degraded. Before the ultimate laser can be realized, the following issues must be addressed: (i) Optical modes that induce undesired spontaneous emission should be suppressed where possible; (ii) a single-cavity mode with a sufficiently high Q factor (the so-called quality factor of the cavity) and a small modal volume is essential; and (iii) excited carriers should be concentrated to emit light coupled to the single-cavity mode.



Connecting the dots. A high-Q nanocavity (red) is formed in a 2D photonic-crystal slab that inhibits spontaneous emission. Quantum dots embedded in the nanocavity confine electrons (and holes) three-dimensionally and have sharp gain functions. Such a configuration may allow thresholdless laser operation.

Regarding the issue (i), the suppression of spontaneous emission has recently been demonstrated (*2*, *3*). Progress in the development of two-dimensional (2D) photonic-crystal slabs (see the figure) has been integral to this achievement. The 2D slab structure facilitates a quasi–three-dimensional (3D) confinement of photons as a result of the large refractive-index contrast perpendicular to the slab. Although spontaneous emission from light emitters inside the 2D slab structure can be coupled to confined or leaky optical modes, it is possible to couple ~94% of the spontaneous emission to the confined mode. Therefore, the use of a 2D photonic-bandgap structure can inhibit ~94% of the spontaneous emission (*3*). Recent experiments have suppressed the spontaneous-emission rate of this system by roughly the theoretical limit (~15 times) (*6*).

As for the fabrication of appropriate cavity modes, a single mode can be introduced by forming an artificial defect in a 2D photonic-crystal slab (see the figure) (*1*). The modal volume (V) of this defect (nanocavity) can be on the order of a cubic wavelength. When the Q factor of the cavity is sufficiently large, the emission coupled to the single-cavity mode can be substantially enhanced by a factor of Q/V, which is called the Purcell

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effect. When the emission rate in the laser mode is much greater than that coupled to the residual leaky optical modes in the 2D slab, thresholdless operation (*7*) would be possible. Thus, the *Q* factor of the nanocavity is an important measure of the optimization of the desired emission process. Nanocavity *Q* factors have improved from hundreds in 1999–2000 (*8*) to ~50,000 in 2003 (*1*), ~600,000 in 2005 (*9*), and >1 million currently (*10*, *11*). Although *Q* factors of >1 million are not essential for thresholdless lasers, the realization of such ultrahigh-*Q* nanocavities is important to control the interaction between photonic and electronic systems.

Ongoing studies also aim to demonstrate that the carriers stored by the suppression of spontaneous emission can be used to induce emission coupled to the single-cavity mode instead of the residual leaky modes in a 2D slab (*6*). Quantum dots (QDs), which can confine carriers three-dimensionally, are the most promising light emitters to be introduced into nanocavities. This 3D carrier confinement allows nonradiative processes to be suppressed. In addition, the gain curve becomes sharp due to the delta-function–like density of states of QDs (*12*). Furthermore, QDs can reach absorption saturation easily due to their strong nonlinearity, and a high *Q* factor of the nanocavity can be maintained even during the initial stages of the excitation. However, the bottleneck blocking the demonstration of thresholdless operation arises because high-quality QDs can be obtained only by self-assembly methods; hence, the wavelengths and positions of the QDs in the nanocavity are random (see the figure). If the cavity mode is resonant with respect to the wavelength and position of the QD, the Purcell effect occurs (*2*, *13*), and the carriers stored by inhibiting spontaneous emission can be used mostly for emission coupled to the single-cavity mode, allowing thresholdless operation to occur. However, if the wavelengths and positions of QDs are not resonant with the cavity mode, the Purcell effect is suppressed and the emission rate of the cavity mode cannot be improved (*2*), leading to the consumption of excited carriers by emission coupled to the residual leaky modes. Thus, a clear demonstration of thresholdless operation remains to be achieved. Nevertheless, a recent paper (*4*) reported that the self-tuned QD gain effect is feasible, in which nearly thresholdless behavior might be obtained even in the off-resonant case. Although a detailed investigation of this effect is necessary, the report could be useful in addressing the matter of carrier concentration.

Major progress toward the realization of thresholdless nanolasers has clearly been achieved with 2D photonic crystal–based nanocavities and their fusion with QDs. However, to accomplish thresholdless laser operation, more needs to be done, including detailed investigations to clarify the interactions between the nanocavity and QDs in an off-resonant condition, and between individual QDs inside the nanocavity. There also needs to be progress in the development of 3D photonic crystals (*14*, *15*). The suppression of undesired spontaneous emission would be at least 10 to 100 times as great as that in a 2D photonic-crystal slab. Even if the QDs and the nanocavity mode were off-resonant, thresholdless operation would be expected because spontaneous emission coupled to residual leaky modes would be reduced to <0.06 to 0.6%. And finally, we must find an appropriate method of current injection (*16*) by which the *Q* factor of the nanocavity is not degraded. The future looks bright on all these fronts.

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CELL BIOLOGY

Balancing Life-or-Death Decisions

Jiri Bartek and Jiri Lukas

Phosphorylation of transcription factors is crucial to whether DNA damage in a cell results in cell death or repair and survival.

At the heart of the ability to self-replicate lies the cell's cycle machinery that orchestrates the flawless duplication of the genome and cell division. The major driving force of the cell cycle engine is the family of cyclin-dependent kinases (CDKs), enzymes that phosphorylate (add phosphate to) a number of cellular proteins. This modification fuels sequential transitions through the cell division cycle (*1*). Recent exciting discoveries show that CDKs may have yet another critical role in cell physiology—to coordinate cell cycle progression with timely responses to DNA-damaging insults that can threaten genomic integrity and cause devastating diseases such as cancer. The latest insight into this other role is published on page 294 of this issue by Huang and colleagues (*2*). These authors show that CDK-mediated phosphorylation of a transcription factor known as FOXO1 during S phase—the most vulnerable period of the cell cycle, when the 3 billion bases of human genomic DNA must be faithfully replicated—controls a cell's survival under genotoxic stress conditions.

In response to replication stress or DNA damage, cells activate a complex network of factors (*3*, *4*) that silence CDKs and thereby delay or arrest cell cycle progression (the so-called checkpoint pathways), promote DNA repair, or, in the case of irreparable damage, eliminate the potentially hazardous cell by induced cell death (apoptosis) (see the figure). The damage alert triggered by DNA lesions that activate these cellular responses is spread by two signaling modules of the checkpoint kinases ATM and ATR that activate the effector kinases Chk2 and Chk1, respectively (*3*, *4*). A key substrate of Chk1 and Chk2 is the Cdc25A phosphatase. Under normal physiological conditions, this enzyme strips the inhibitory phosphate molecule from CDK2, thereby activating it. CDK2 regulates the G_1-S transition and S-phase progression of the cell division cycle. After DNA damage or stalling of DNA replica-

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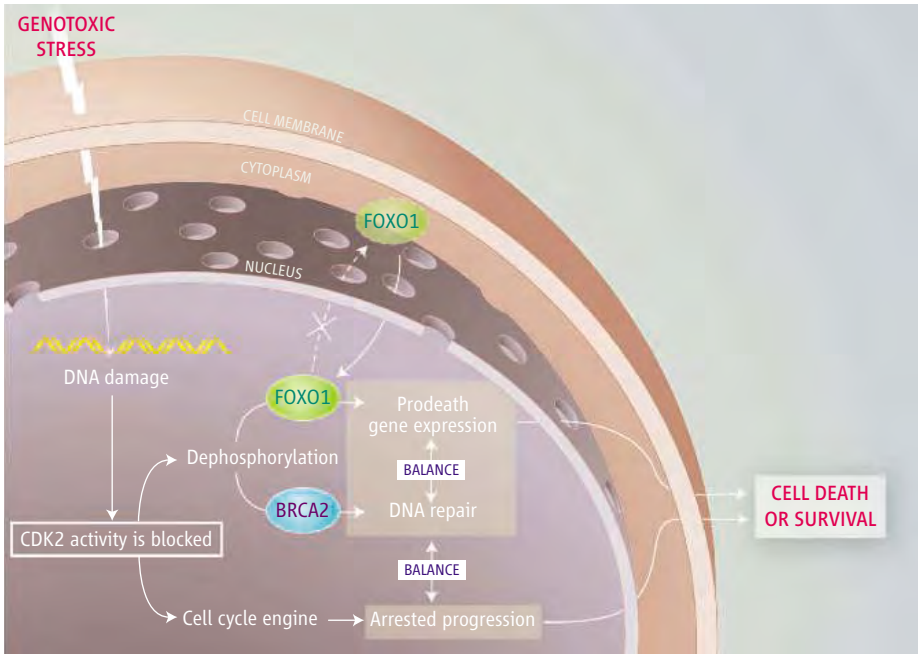

Cell fate decisions after DNA damage. In response to DNA lesions, CDK2 is inhibited, thereby withdrawing the CDK-mediated protection from unwanted death or DNA recombination. As a result, a cell may coordinately stall cell cycle progression and activate factors that allow cells to repair DNA by recombination (BRCA2) and survive, or trigger cell death (FOXO1). How the equilibrium between a productive repair (followed by a return into the cell cycle) and cell death is achieved remains unclear.

tion, Chk1/Chk2-mediated phosphorylation of Cdc25A triggers rapid degradation of the phosphatase by the proteasome (*4*). The resulting inhibition of CDK2 then plays a central role in DNA damage–activated cell cycle arrest (*4*) and DNA repair (*5*). However, it has been unknown whether CDK2 also influences cell survival, an issue elucidated in the new work by Huang *et al*.

In search of a possible link between CDK2 and regulation of cell death, Huang *et al*. identified FOXO1, the transcriptional activator of proapoptotic genes (*6*), as a substrate of CDK2. During unperturbed S phase, CDK2 phosphorylates FOXO1 on a serine residue (Ser^{249}) in a region that localizes the transcription factor to the nucleus. This modification sequesters FOXO1 in the cytoplasm, away from its nuclear target proapoptotic genes. When cells are exposed to insults that cause DNA damage, CDK2 becomes inhibited through the Cdc25A degradation pathway (*4*), resulting in dephosphorylation of FOXO1-Ser^{249}, subsequent nuclear localization of FOXO1, and activation of genes that promote cell death. When FOXO1 expression was down-regulated by small interfering RNA–mediated knockdown, or when a FOXO1 mutant that mimics its serine-phosphorylated form was expressed, cells exposed to DNA-damaging drugs or radiation were prevented from dying. In contrast, when CDK2 activity was neutralized by either a small-molecule inhibitor or the expression of a FOXO1 mutant that is not phosphorylated by CDK2, the nuclear localization of FOXO1 and cell death increased.

These elegant experiments and those on the role of CDK2-mediated regulation of DNA repair by homologous recombination (*5*) illustrate an emerging role for CDKs in orchestrating cell fate decisions in response to genotoxic stress. During unperturbed DNA replication, CDK-mediated phosphorylation of the transcription factors BRCA2 (*5*) and FOXO1 (*2*) renders the DNA recombination and cell death mechanisms, respectively, temporarily inactive, yet ready to step in when cells encounter DNA damage and cell cycle progression is blocked through the CDK-silencing checkpoint cascades. In addition, other aspects of genome integrity maintenance, such as processing the ends of broken DNA (*7*) or recruitment and assembly of additional factors to sites of DNA damage (*8*), appear to be controlled by analogous CDK-mediated phosphorylations. Given the many pathways that respond to DNA damage, the list of CDK substrates involved in processes that coordinate cell cycle progression with the emergency responses is likely to grow.

As Huang *et al*. point out, their work also has important implications for understanding cancer pathogenesis and disease management. In cancer, CDK2 activity is commonly deregulated and the DNA damage response machinery that was recently identified as a barrier against oncogene-driven progression of early human lesions to malignancy (*9*, *10*) is often defective (*3*). Both unscheduled CDK2 activity and malfunction of the genome maintenance mechanisms may lead to inefficient induction of cell death, and hence to aberrantly enhanced resistance to widely used DNA-damaging treatments including ionizing radiation and chemotherapy.

These new discoveries raise a host of questions. What ensures that FOXO1-mediated apoptosis (*2*) or BRCA2-mediated genome repair (*5*) in response to DNA breaks occur during the S phase, but not in the G_1 phase, of the cell cycle? For BRCA2, we know that the high CDK activity needed to allow processing of DNA breaks is unavailable in the G_1 phase (*7*). Similarly, CDKs could also restrict FOXO1-induced cell death because phosphorylation of an additional target(s) in the pathway is required for efficient expression or accumulation of proapoptotic effectors. Also, given that both BRCA2-mediated DNA repair and cell death pathways are activated upon silencing of CDK activity in response to DNA damage, what determines the duration and final outcome of such processes? Perhaps a longer persistence of CDK2-mediated phosphorylations, such as FOXO1-Ser^{249} (*2*), and the requirement for transcription and subsequent accumulation to threshold levels of the FOXO1-regulated factors, give a cell the chance to repair the damage and resume proliferation. Does transient activation of a pro-survival transcription program by the DNA damage machinery itself, such as the ATM–NEMO–nuclear factor κB cascade (*11*), open a transient window of opportunity for a successful repair before cell death prevails? Understanding how cells balance life-and-death decisions may help us to ultimately save patients' lives.

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GEOCHEMISTRY

How Fast Does Gold Trickle Out of Volcanoes?

The enormous hydrothermal gold ore deposit on Lihir Island, Papua Guinea, may have formed in less than 55,000 years.

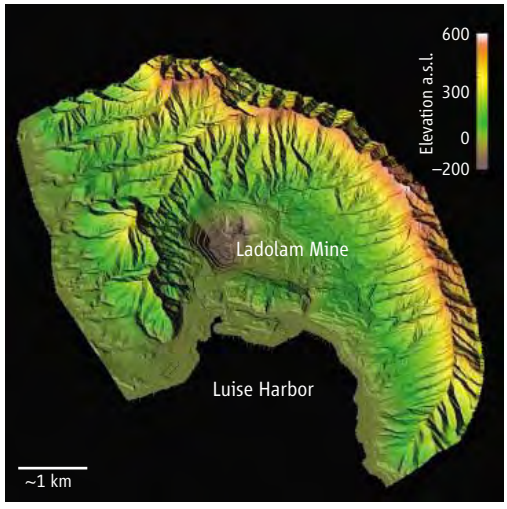
Christoph A. Heinrich

Economic resources of many valuable metals—including zinc, copper, and gold—form by selective enrichment when water-rich fluids circulate through large volumes of Earth's crust. The fluids extract trace-level concentrations of the metals from rocks or partly molten magmas and deposit them in a smaller volume of rock under specific physical and chemical conditions. Ore bodies formed in this way are worth billions of dollars, but great geological and technical skills are required to find them and develop them into environmentally sound mining operations.

Most economic ore bodies formed in the distant geological past, and some are covered by younger, barren rock. A precise understanding of the process of ore formation is therefore key to discovering new resources. On page 288 of this issue, Simmons and Brown (*1*) report the chemical composition of fluids circulating through a giant gold ore-body located in the center of a geothermally active volcano: the Ladolam deposit on Lihir Island, Papua New Guinea (see the first figure). Direct analyses of the gold concentration in these recent fluids demonstrate an intimate link of ore formation to magmatic processes and indicate that metal enrichment occurred in a geologically short period of time. The authors imply that gold mineralization may even go on today, while ore is mined from steaming hot ground in a giant open cut (see the second figure).

Recent debate about magmatic-hydrothermal ore formation has focused on two issues (*2*). The first concerns the origin of the required ore fluid. Is surface-derived water, circulating deeply and heated passively by subjacent magma intrusions, sufficient to leach metals from solid rocks and make an ore deposit? Or do chemically specialized magmatic fluids, expelled from crystallizing magma and already pre-enriched in ore metals, make the key difference between an ordinary geothermal system and a real ore deposit?

The second issue relates to the dynamics of the ore-forming process. If magmatic fluids are indeed essential (as indicated by recent fluid-inclusion, isotopic, and solubility data), how do the fluids evolve, physically and chemically, en route from the magma to the site of ore-mineral deposition? How much fluid is required to form a major ore deposit, and how long does the process take—centuries or millions of years?



Part of the island of Lihir, looking south-southwest. The former Luise Volcano collapsed toward Luise Harbor in front of the picture. This sector collapse left as a relict the before prominent semicircle of mountains, before the formation of the Ladolam gold deposit. This digital elevation model has been modified from (*7*); the scale is approximate due to perspective representation. a.s l., above sea level.

To address these questions, Simmons and Brown have obtained complete and undisturbed samples of deep magmatic fluids extracted from fractured rocks located more than a kilometer beneath the Ladolam ore deposit. In situ fluid sampling at depth, using a prototype probe lowered into deep boreholes, is essential to their study, because the composition of fluids changes during their natural flow toward Earth's surface. As the fluid ascends through fractured rocks or in open boreholes, the pressure decreases, resulting in boiling and loss of volatile components from the aqueous solution. In particular, sulfur, in the form of H_2S and HS^-, is lost in this way; this is important because it is required to keep gold in solution as a transportable gold bisulfide complex.

Oxygen and hydrogen isotopes indicate that the deep fluids have a mainly magmatic origin (*3*). Simmons and Brown discovered that the fluids contain higher gold concentrations than observed in other active geothermal systems. The authors compared their analytical results with experimental solubility limits for the analyzed H_2S content. The results indicate that the deep fluid is slightly gold-undersaturated at high pressure, but will reach conditions of gold precipitation by natural decompression and volatile loss during its ascent to the tabular ore body closer to Earth's surface. Given the geothermal heat flow caused by the ascending fluids and their initial gold content, Simmons and Brown calculate that it took 55,000 years to accumulate the 1600 metric tons of gold now contained in the Ladolam deposit.

These results open up new questions and will stimulate the ongoing debate about the connection between magmatism, geothermal activity, and ore formation. Based on our own studies of other mineral deposits, the concentrations of 10 to 20 mg of gold in a liter of fluid measured by Simmons and Brown seem quite modest. Microanalysis of inclusions of ancient ore fluids (*4*) has shown the existence of gold in high-temperature, vapor-like fluids of similar salinity at concentrations that are 100 to 1000 times as high as those measured by Simmons

The Ladolam Mine. To extract ore from the fluid-saturated ground of this mine, the ground must be cooled artificially by water injection and steam release. According to Simmons and Brown, the active magmatic-hydrothermal system at the Ladolam mine could have formed the large gold ore deposit over the past tens of thousands of years.

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and Brown. These high gold concentrations can be kept in solution during cooling, provided that the fluids have much higher sulfide contents than those observed at Ladolam today (*5*).

The active geothermal waters beneath Ladolam are of magmatic origin and sulfate-rich, yet they contain far less sulfide than expected from the disproportionation of SO_2 (the dominant form of sulfur in high-temperature aqueous fluids exsolving from magmas) to its lower-temperature products, SO_4^{2-} and H_2S (*6*). This may indicate that a much larger fraction of H_2S or sulfide was originally present in the magmatic fluid, but was lost well before the present geothermal system was established.

In light of the geological history of Lihir (*3*), these observations are consistent with a story for the formation of the giant Ladolam deposit that is even more spectacular than the one envisaged by Simmons and Brown. Most of its gold ore is contained in minerals cementing a highly fragmented rock, which was produced by a dramatic event about half-a-million years ago, when the peak of a former volcano built high above the present area of the deposit collapsed and formed the present semicircle of mountains around the deposit (see the first figure). This sector collapse would have led to sudden decompression of magmatic-hydrothermal fluids beneath the volcano, which originally could have been orders of magnitudes more gold- and sulfur-rich.

Could a rush of rapidly expanding fluids have formed the deposit in an even shorter period of time than calculated by Simmons and Brown, just after this dramatic event and maybe even on the time scale of a human life? And could the extraordinary geothermal waters sampled today be a mere trickle representing the "spent" ore fluid, still circulating through the rocks half-a-million years after the rush of fluids that formed the deposit?

Precise radiometric dating of mineral deposition may help to answer these questions, but the interpretation of such data could be challenging. The rocks have been kept at high temperature to the present day, potentially allowing all isotopic clocks to reset themselves continually. But there is no doubt that further study of this unique hydrothermal ore system may hold the key to understanding the link between volcanism and the formation of mineral resources.

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CHEMISTRY

Strong-Arming Molecular Dynamics

Guided laser pulses can be used to shift the path of a chemical reaction. Such control is turning out to be much easier than originally thought.

Herschel Rabitz

Rearranging or substituting atoms in molecules is at the heart of chemistry's role in the sciences. Traditionally, these operations have been performed with chemical reagents, but a long-standing dream has been to use tailored laser pulses acting as photonic reagents to stimulate and redirect such chemical transformations—or, even more generally, to perform quantum state manipulations in virtually any material (*1*). Control of quantum phenomena, especially in complex systems such as polyatomic molecules, is primarily being done with rapidly shaped ultrafast laser pulses linked with pattern recognition software that monitors the outcome (*2*–*4*). The process is repeated many times under guidance of the software to discover precisely the proper photonic reagents for best achieving desired atomic- or molecular-scale quantum mechanical transformations, including chemical reactions.

Redirecting atomic-scale quantum mechanical events, especially to create products that could not be achieved naturally, entails having the photonic reagents go head-to-head in competition with the intrinsic interatomic forces. Although a successful photonic reagent must carry with it sufficient energy to make the desired transformation, that energy might be distributed over many periods of atomic-scale motion. However, intuition suggests that having the photonic reagent interact with the sample in a fast and furious fashion is the best way to compete with the interatomic forces and to overcome deleterious side effects. Such laser pulse strong-arming of molecular motion has long been thought attractive for manipulating quantum phenomena and especially for redirecting chemical reactions, but until now little evidence has existed for its actual role. On page 278, Sussman *et al.* (*5*) report that strong laser field effects can be isolated from other possible competing processes, and they provide clear evidence that intense laser pulse manipulation of quantum mechanical events can be quite effec-

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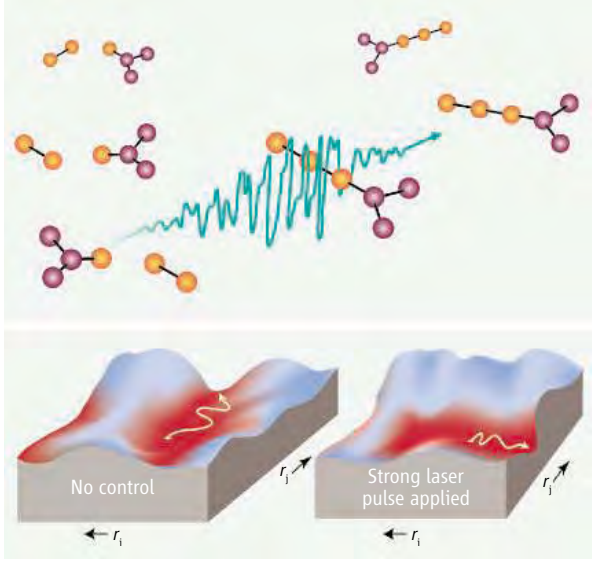

Photonic reagent chemistry. (**Top**) As the electric field of the laser pulse (green) interacts with the molecules, its tailored shape overcomes the natural interatomic forces and selectively dissociates the molecules. (**Bottom**) A portion of the molecule's potential energy landscape as a function of the generic coordinates r_i and r_j. The molecule dissociates by taking the indicated paths. Left: Under no photonic reagent control (e.g., through the simple application of heat), the molecule typically dissociates by breaking the weakest bond. Right: Upon application of a tailored photonic reagent, the energy landscape is distorted to open up a new favorable product channel, as indicated by the altered trajectory taken.

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tive at the atomic scale and likely have generic value across many applications.

In these experiments, the photonic reagent–induced forces arise through the Stark effect, whereby the electric field of the laser pulse interacts with the electrons in a molecule to severely disrupt their natural behavior and, as a result, distort the energy landscape structure of the molecule (see the figure). If this distortion can be carried out properly, a chemical reaction or other type of molecular transformation may be steered in a direction it might not ordinarily evolve in. In the present case (*5*), this redirection was achieved in the controlled dissociation of the diatomic molecule IBr to form the products I + Br or I + Br*, where Br* is an excited state of the bromine atom. The control goal was to steer the reaction from either of these product channels to the other by applying a suitable strong laser pulse that operates by manipulating the forces between the atoms.

The evidence for this control mechanism arises from the fact that the applied intense radiation pulse is not resonant with any of the molecule's natural transition frequencies, thereby preventing any direct absorption of the pulse energy in a conventional way. Thus, the steering from one product to the other can be understood to result from strong-armed manipulation of the energy landscape structure of IBr. For this system, the general energy landscape distortion shown in the figure now reduces to the manipulation of one-dimensional potential energy curves (because there is only a single chemical bond). The physical process may be viewed as photonic reagent–driven catalysis—by analogy with the operation of ordinary chemical catalysts that open up some product channels while closing others—although in the present case the photonic reagent catalysts have a fleeting existence.

This clear experimental illustration (*5*) of strong laser field manipulation of molecular energy landscape structure as a means for control may be extended to polyatomic molecules or other materials far more complex than IBr, and the generic process is illustrated in the figure. In recent years, many studies have been carried out with photonic reagents selectively breaking bonds and otherwise creating tailored excitations in atoms and molecules (*3*). The actual mechanisms by which the photonic reagents act on molecules are only just beginning to be revealed (*6*). Whenever the fields are strong to produce forces competitive with those naturally existing, then Stark shifting of the energy landscape structure should play a role in the control mechanism.

Experiments that manipulate quantum dynamics phenomena often operate by first separating the broad-bandwidth frequency components in a raw unshaped laser pulse and then gaining control over the phase and amplitude of each frequency component (*2*–*4*, *6*). The desired photonic reagent is created through the adjustment of typically hundreds of laser phase and amplitude "knobs" within the bandwidth of the pulse to achieve just the right structure for the photonic reagent to push and pull on a molecule's electrons in an orchestrated fashion to achieve the desired target objective. The shaping of the laser pulse is achieved with feedback guidance from observation of the controlled outcome (e.g., a particular quantum state or reaction product) with the aim of taking advantage of every opportunity offered by pulse shaping to better reach the desired goal. The resultant optimal photonic reagents often have quite complex temporal structure forming resonant and nonresonant interactions with a molecule, encompassing weak and strong field effects, all interspersed during the period that the pulse is on.

Identifying the correct settings for the hundreds of laser knobs to produce an effective photonic reagent is proving to be surprisingly easy, despite what might be thought of as a formidable search through the high-dimensional space of phase and amplitude control variables. Arguments at the foundations of quantum mechanics provide a means to understand the evident relative ease of designing successful laser pulses (*7*) for controlling transformations. This finding, along with the established ability to rather freely strong-arm atomic and molecular landscapes (*5*) as well as perform manipulations in the lower laser intensity regime (*8*), now provides both the basis and the means to fully explore the fundamental science of controlling quantum phenomena and its potential technological implications.

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CHEMISTRY

Quantum Chemistry of Complex Systems

David C. Clary

Progress in developing quantum chemical calculations that describe complex atomic systems has applications in molecular biology, materials science, and chemistry.

In 1926, Erwin Schrödinger first derived the analytical solutions for the electronic states of the hydrogen atom (*1*). Not long after this, Paul Dirac said: "The underlying physical laws necessary for the mathematical treatment of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble. It therefore becomes desirable that approximate practical methods of applying quantum mechanics should be developed, which can lead to an explanation of the main features of complex atomic systems without too much computation" (*2*).

What progress has been achieved, some 80 years later, in applying quantum mechanics to complex atomic systems? A symposium at the first European Chemistry Congress in Budapest in August of this year (*3*) provided a snapshot of the progress in this field. Invited talks by Hans-Joachim Werner, Michael A. Robb, and Evert J. Baerends illustrated the current capabilities of quantum chemistry.

It is only for one-electron systems, such as the hydrogen atom, that Schrödinger's equation has an exact analytical solution. Even for two-electron molecules such as H_2, numerical solutions are needed. Progress in the applicability of quantum chemistry has therefore depended on advances in computer power. It is now possible, using readily available computer packages, to calculate the energies and properties of many small molecules to an accuracy that can rival that obtained experimentally. This advance has been achieved

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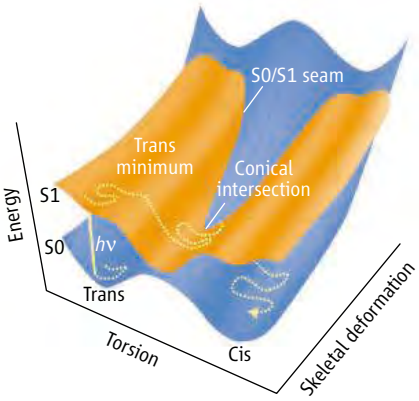
through the development of theories and computational techniques that provide a rigorous description of electron motion (orbitals) and correlated interactions of electrons. The challenge is to extend these methods and computer programs to solving the Schrödinger equation for systems such as the very large molecules and nanostructures of interest in biology and materials science.

Werner clearly defined the main bottleneck that has prevented accurate electronic structure calculations from being applied to large molecules: the prohibitive scaling of computational cost with the number of electrons (N) in a molecule. This scaling is N^7 for conventional methods, which allow for the correlation of all pairs of electrons in a molecule. Werner and co-workers are one of the groups that have developed powerful methods that allow only electrons close to each other to be correlated; this allows for "linear scaling," that is, a dependence in computational cost on N (*4*).

The accurate description of electron orbitals in molecules also presents difficulties, with the computer time depending on N_A^4 in conventional methods, where N_A is the number of basis functions used to describe an electron. A recently developed "density fitting" procedure has reduced this dependence to N_A (*5*). Another advance that improves the accuracy of the calculations is the explicit inclusion of the interelectronic distance in the wave functions used in these approaches (*6*).

These computational developments allow accurate quantum chemistry to be extended to molecular systems with many more atoms than was possible previously. Werner described recent calculations of an energy barrier that compares very well with experiment for the structural rearrangement of the enzyme chorismate mutase; the method has also been applied to the antiretroviral drug indinavir. This approach has tremendous promise for addressing many problems in biochemistry and molecular biology.

Many key processes involving molecules, including photosynthesis and the reception of light by the eye, involve electronically excited states, and quantum chemists have been making substantial progress in applying their methods to this type of problem. Robb described progress by his group in developing methods to understand "conical intersections," the molecular geometries in which two different electronic states meet and allow for efficient energy transfer. His group has addressed an exciting range of problems, including the photochemical conversion of the photochromic material merocyanine to spiropyran (*7*) and the ultrafast internal conversion of pyracylene (*8*). By factoring out the essential reaction coordinate, he and his co-workers have explained how light triggers an isomerization in the chromophore of the photoactive yellow protein (see the figure) (*9*). A few years ago, this problem would have been beyond the reach of quantum chemistry.



New light from quantum chemistry. Calculations provide insight into the mechanism by which isomerization of the photoactive yellow protein is triggered by blue light ($h\nu$). The molecule is excited to the S1 state and is able to deform and move to the ground electronic S0 state via the conical intersection. The dotted yellow line represents the path sampled in this process (*9*).

Understanding chemical reactions that occur on solid surfaces is an area of vital importance in industry. The production of ammonia from nitrogen and hydrogen on metal catalysts is a classic example, and more than 1% of global energy consumption is used to enable this vital reaction to proceed. Optimizing the efficiency of these catalysts is thus essential.

This problem can now be addressed with the methods of quantum chemistry and quantum dynamics (*10*, *11*). For example, Baerends and his group have used density functional theory (DFT) to understand how molecules interact with metals and, in particular, how the energy barrier to reaction is reduced by catalysis on a metal surface. DFT is not as accurate as the electron correlation approaches used by Werner and others, but this general method can be readily applied to many-electron systems such as molecules on metals.

A clear explanation for the action of metal catalysts remains a subject of some debate. Baerends and co-workers have produced an elegant analysis of this problem, illustrating that quantum chemistry is important not only for producing useful numbers but also for providing concepts in catalysis (*12*). Energy barriers in chemical reactions are partly produced by electron repulsion. This is minimized—Baerends and co-workers argue—through escape of antibonding electrons to previously unoccupied energy levels. This is the crucial feature that causes molecule-metal bond energies to be stronger, and dissociation barriers of adsorbed molecules to be much lower, than in systems with no or one metal atom.

A complete description of molecular systems requires consideration not only of the electronic structure, but also of the dynamics of the atoms in molecules. The latter is essential for the simulation of molecular processes such as chemical reactions. Atom motion can be followed fairly routinely with classical molecular dynamics, but the challenge is to develop general quantum dynamical methods that allow for key quantum effects such as tunneling through a potential barrier.

Solving the Schrödinger equation for nuclei taking part in molecular transformations is therefore a frontier area of modern theoretical chemistry (*13*). For such quantum dynamics methods to be widely applicable, they must be combined with accurate electronic structure techniques for calculating potential energy surfaces, such as those developed by Werner and co-workers. Progress in this direction was discussed at the conference, which heard that large tunneling effects observed in chemical reactions of hydrogen atoms with a variety of hydrocarbons can now be calculated accurately (*14*).

The presentations at the conference represent only a small fraction of the major efforts that are being made in laboratories around the world to bring Dirac's vision to reality. The availability of increasingly powerful computers has been crucial to the progress in this field. The continuing development of ingenious theories and computational algorithms has also been essential in moving toward the ability to make accurate predictions on complex atomic and molecular systems.

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The 160-Kilobase Genome of the Bacterial Endosymbiont *Carsonella*

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Many bacterial lineages have evolved mutually obligate endosymbiotic associations with animal hosts. In such cases, the bacteria typically produce essential nutrients that are rare in the host diet, and the animal produces specialized cells (bacteriocytes) where bacteria are confined and, like organelles, continuously maintained through vertical transmission across host generations. These bacteriocyte-restricted bacteria have distinctive genomic features, including massive reduction in genome size and biased nucleotide base composition (*1*). However, all cases of genome reduction appear to reach limits of about 400 kb and about 20% GC, which are believed to be the minimal limits for cellular organisms (Fig. 1).

Here, we present a genome that has evolved far beyond these limits. *Carsonella ruddii* (Fig. 1) is a bacteriocyte-associated γ-proteobacterial symbiont that appears to be present in all species of phloem sap-feeding insects, psyllids (*2*). We determined the complete genome sequence of *C. ruddii* strain Pv (*Carsonella*-Pv) of the hackberry petiole gall psyllid, *Pachypsylla venusta*, which has no other microbial symbionts (*2*). The genome of *Carsonella*-Pv is a single circular chromosome of 159,662 base pairs (bp), averaging 16.5% GC content. The assembly analysis, using a large excess of sequence data, did not reveal any other symbionts or plasmids. The genome size, which was further confirmed by long-range electrophoresis, is only about one-third that of the archaeal parasite *Nanoarchaeum equitans* (having the smallest fully sequenced genome to date, at 491 kb) (*3*) and that of an unsequenced *Buchnera* strain (having the smallest known bacterial genome, at about 450 kb) (*4*).

The genome has only 182 open reading frames (ORFs) (fig. S1A), which were classified into the clusters of orthologous groups (COGs). Notably, more than half of ORFs are devoted to only two categories, translation (34.6%) and amino acid metabolism (17.6%) (fig. S1B). In the latter, *Carsonella* retains many genes for biosynthesis of essential amino acids, as in *Buchnera*, the symbiont of aphids. Because both psyllids and aphids feed only on plant phloem sap that is poor in essential amino acids, the analogy of gene repertoires in *Carsonella* and *Buchnera* is an intriguing example of convergence. A remarkable feature of the genome is the total loss of genes for numerous categories, including cell envelope biogenesis and metabolisms of nucleotides and lipids (fig. S1B).

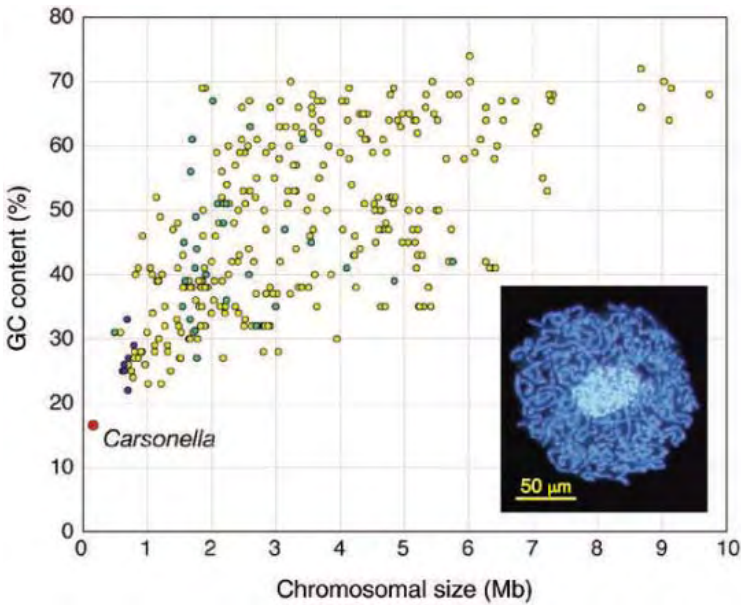

Fig. 1. Relationship between genome sizes and GC content of 358 complete genomes from Bacteria and Archaea: red indicates *Carsonella*; blue represents endosymbionts *Buchnera*, *Blochmannia*, *Wigglesworthia*, and *Baumannia*; yellow, other Bacteria; and green, Archaea. **(Inset)** A 4′,6′-diamidino-2-phenylindole–stained bacteriocyte of *P. venusta*. Tubular cells surrounding the host nucleus (center) are *Carsonella*.

Another feature of this genome is an extremely high gene density. The protein-coding sequences and RNA genes (one 16S-23S-5S ribosomal RNA operon and 28 tRNA genes for all 20 amino acids) cover 97.3% of the genome, which is a gene density higher than those in known bacterial genomes. This density is attributable to numerous overlapping genes. Of 182 ORFs, 164 (90%) overlap with at least one of the two adjacent ORFs, and the average length of all 132 overlaps is 10.7 bases. The majority (92%) are tandem overlaps on the same strand, all of which are out of frame. Moreover, the average length of *Carsonella* ORFs (826 bp) is notably shorter than that of other bacteria. Indeed, a comparison of 89 orthologous ORFs conserved in *Carsonella* and in seven bacteriocyte-restricted endosymbionts revealed that the average length of the ORFs in *Carsonella* is 17.8 to 18.4% shorter than the average ORF lengths of the other endosymbionts.

This genome is by far the most streamlined studied to date. Its gene inventory seems insufficient for most biological processes that appear to be essential for bacterial life, and possibly the host bacteriocyte compensates. Although some psyllids possess additional secondary endosymbionts that might be a source of specialized gene products, no other symbionts are present in *P. venusta*, based on several lines of evidence [e.g., (*2*)]. The genome also lacks many genes for bacterium-specific processes. One of several possible explanations for the absence of these genes is that, as in the case of organelles (*5*), some genes were transferred from the genome of a *Carsonella* ancestor to the genome of a psyllid ancestor and are now expressed under control of the host nucleus.

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Supporting Online Material

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Fig. S1
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The Consensus Coding Sequences of Human Breast and Colorectal Cancers

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The elucidation of the human genome sequence has made it possible to identify genetic alterations in cancers in unprecedented detail. To begin a systematic analysis of such alterations, we determined the sequence of well-annotated human protein-coding genes in two common tumor types. Analysis of 13,023 genes in 11 breast and 11 colorectal cancers revealed that individual tumors accumulate an average of ~90 mutant genes but that only a subset of these contribute to the neoplastic process. Using stringent criteria to delineate this subset, we identified 189 genes (average of 11 per tumor) that were mutated at significant frequency. The vast majority of these genes were not known to be genetically altered in tumors and are predicted to affect a wide range of cellular functions, including transcription, adhesion, and invasion. These data define the genetic landscape of two human cancer types, provide new targets for diagnostic and therapeutic intervention, and open fertile avenues for basic research in tumor biology.

It is widely accepted that human cancer is a genetic disease caused by sequential accumulation of mutations in oncogenes and tumor suppressor genes (*1*). These tumor-specific (that is, somatic) mutations provide clues to the cellular processes underlying tumorigenesis and have proven useful for diagnostic and therapeutic purposes. To date, however, only a small fraction of the genes has been analyzed, and the number and type of alterations responsible for the development of common tumor types are unknown (*2*). In the past, the selection of genes chosen for mutational analyses in cancer has been guided by information from linkage studies in cancer-prone families, identification of chromosomal abnormalities in tumors, or known functional attributes of individual genes or gene families (*2*–*4*). With the determination of the human genome sequence and recent improvements in sequencing and bioinformatic approaches, it is now possible in principle to examine the cancer cell genome in a comprehensive and unbiased manner. Such an approach not only provides the means to discover other genes that contribute to tumorigenesis, but also can lead to mechanistic insights that are only evident through a systems biological perspective. Comprehensive genetic analyses of human cancers could lead to discovery of a set of genes, linked together through a shared phenotype, that point to the importance of specific cellular processes or pathways.

To begin the systematic study of the cancer genome, we examined a major fraction of human genes in two common tumor types, breast and colorectal cancers. These cancers were chosen for study because of their substantial clinical importance worldwide; together they account for ~2.2 million cancer diagnoses (20% of the total) and ~940,000 cancer deaths each year (14% of the total) (*5*). For genetic evaluation of these tumors, we focused on a set of protein-coding genes, termed the consensus coding sequences (CCDS), that represent the most highly curated gene set currently available. The CCDS Database (*6*) contains full-length protein-coding genes that have been defined by extensive manual curation and computational processing and have gene annotations that are identical among reference databases.

The goals of this study were (i) to develop a methodological strategy for conducting genome-wide analyses of cancer genes in human tumors, (ii) to determine the spectrum and extent of somatic mutations in human tumors of similar and different histologic types, and (iii) to identify new cancer genes and molecular pathways that could lead to improvements in diagnosis or therapy.

Cancer mutation discovery screen. The initial step toward achieving these goals was the development of methods for high-throughput identification of somatic mutations in cancers. These methods included those for primer design, polymerase chain reaction (PCR), sequencing, and mutational analysis (Fig. 1). The first component involved extraction of all protein-coding sequences from the CCDS genes. A total of 120,839 nonredundant exons and adjacent intronic sequences were obtained from 14,661 different transcripts in CCDS. These sequences were used to design primers for PCR amplification and sequencing of exons and adjacent splice sites. Primers were designed using a number of criteria to ensure robust amplification and sequencing of template regions (*7*). Although most exons could be amplified in a single PCR reaction, we found that exons larger than 350 base pairs (bp) were more effectively amplified as multiple overlapping amplicons. One member of every pair of PCR primers was tailed with a universal primer sequence for subsequent sequencing reactions. A total of 135,483 primer pairs encompassing ~21 Mb of genomic sequence were designed in this manner (table S1).

Eleven cell lines or xenografts of each tumor type (breast and colorectal carcinomas) were used in the discovery screen (table S2, A and B). Two matching normal samples were used as controls to help identify normal sequence variations and amplicon-specific sequencing artifacts such as those associated with GC-rich regions. A total of ~3 million PCR products were generated and directly sequenced, resulting in 465 Mb of tumor sequence.

Sequence data were assembled for each amplicon and evaluated for quality within the target region with the use of software specifically designed for this purpose (*7*). The target region of each exon included all coding bases as well as the four intronic bases at both the 5′ and 3′ ends that serve as the major splice recognition sites. For an amplicon to be considered successfully analyzed, we required that ≥90% of bases in the target region have a Phred quality score—defined as $-10[\log_{10}(\text{raw per-base error})]$—of at least 20 in at least three-quarters of the tumor samples analyzed (*8*). This quality cutoff was chosen to provide high sensitivity for mutation detection while minimizing false positives. Using these criteria, 93% of the 135,483 amplicons and 90% of the total targeted bases in CCDS were successfully analyzed for potential alterations.

Examination of sequence traces from these amplicons revealed a total of 816,986 putative

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nucleotide changes. Because the vast majority of changes that did not affect the amino acid sequence (i.e., synonymous or silent substitutions) were likely to be nonfunctional, these changes were not analyzed further. The remaining 557,029 changes could represent germline variants, artifacts of PCR or sequencing, or bona fide somatic mutations. Several bioinformatic and experimental steps were used to distinguish among these possibilities. First, any alterations that were also present in either of the two normal samples included in the discovery screen were removed, as these were likely to represent common germline polymorphisms or sequence artifacts. Second, as these two normal control samples would be expected to contain only a subset of known variants, any change corresponding to a germline polymorphism found in single-nucleotide polymorphism (SNP) databases was also removed (*7*). Finally, the sequence trace of each potential alteration was visually inspected so as to remove false positive calls in the automated analysis. The combination of these data analysis efforts was efficient, removing ~96% of the potential alterations and leaving 29,281 for further scrutiny (Fig. 1).

To ensure that the observed mutations did not arise artifactually during the PCR or sequencing steps, we independently reamplified and resequenced the regions containing them in the corresponding tumors. This step removed 9295 alterations. The regions containing the putative mutations were then sequenced in matched normal DNA samples to determine whether the mutations were truly somatic: 18,414 changes were observed to be present in the germ line of these patients, representing variants not currently annotated in SNP databases, and were excluded. As a final step, the remaining 1572 putative somatic mutations were carefully examined in silico to ensure that the alterations did not arise from mistargeted sequencing of highly related regions occurring elsewhere in the genome (*7*). Alterations in such duplicated regions may appear to be somatic when there is loss of one or both alleles of the target region in the tumor and when the selected primers closely match and therefore amplify similar areas of the genome. A total of 265 changes in closely related regions were excluded in this fashion, resulting in a total of 1307 confirmed somatic mutations in 1149 genes (Table 1).

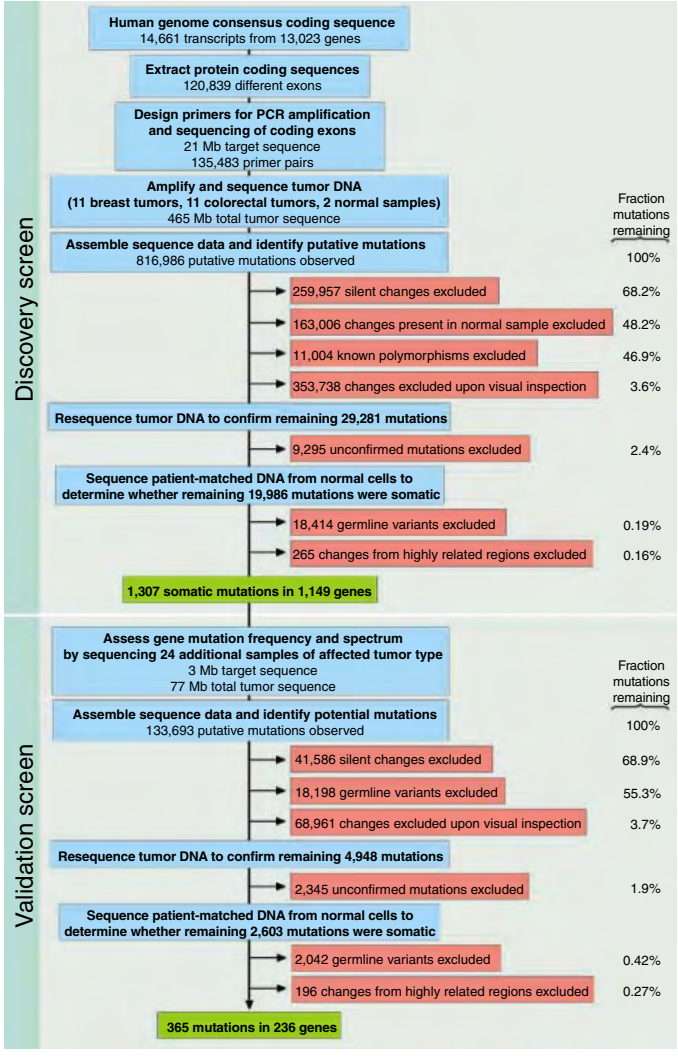

Fig. 1. Schematic of mutation discovery and validation screens.

Validation screen. To evaluate the prevalence and spectrum of somatic mutations in these 1149 genes, we determined their sequence in additional tumors of the same histologic type (Fig. 1) (table S2, A and B). Genes mutated in at least one breast or colorectal tumor in the discovery screen were analyzed in 24 additional breast or colorectal tumors, respectively. This effort involved 453,024 additional PCR and sequencing reactions encompassing 77 Mb of tumor DNA. A total of 133,693 putative changes were identified in the validation screen. Methods similar to those used in the discovery screen were used to exclude silent changes, known and novel germline variants, false positives arising from PCR or sequencing artifacts, and apparent changes that were likely due to coamplification of highly related genes. Additionally, any changes corresponding to germline variants not found in SNP databases but identified in the discovery screen were excluded. The regions containing the remaining 4948 changes were reamplified and resequenced in the corresponding tumors (to ensure reproducibility) and in matched normal tissue to determine if they were somatic. An additional 365 somatic mutations in 236 genes were identified in this manner. In total, 921 and 751 somatic mutations were identified in breast and colorectal cancers, respectively (Fig. 1, Table 1, and table S4).

Mutation spectrum. The great majority of the 1672 mutations observed in the discovery or validation screens were single base substitutions: 81% of the mutations were missense, 7% were nonsense, and 4% were altered splice sites (Table 1). The remaining 8% were insertions, deletions, and duplications ranging from 1 to 110 nucleotides in length. Although the fraction of mutations that were single base substitutions was similar in breast and colorectal cancers, the spectrum and nucleotide contexts of the substitution mutations were very different between the two tumor types. The most striking of these differences occurred at C:G base pairs: 59% of the 696 colorectal cancer mutations were C:G to T:A transitions, whereas only 7% were C:G to G:C transversions (Table 2 and table S3). In contrast, only 35% of the mutations in breast cancers were C:G to T:A transitions, whereas 29% were C:G to G:C transversions. In addition, a large fraction (44%) of the mutations in colorectal cancers were at 5′-CpG-3′ dinucleotide sites, but only 17% of the mutations in breast cancers occurred at such sites. This 5′-CpG-3′ preference led to an excess of nonsynonymous mutations, resulting in changes of arginine residues in colorectal cancers but not in breast cancers (fig. S1). In contrast, 31% of mutations in breast cancers occurred at 5′-TpC-3′ sites (or complementary 5′-GpA-3′ sites), whereas only 11% of mutations in colorectal cancers occurred at these dinucleotide sites. The differences noted above were all highly significant ($P < 0.0001$) (*7*) and have substantial implications for the mechanisms underlying mutagenesis in the two tumor types.

Distinction between passenger and nonpassenger mutations. Somatic mutations in

human tumors can arise either through selection of functionally important alterations (via their effect on net cell growth) or through accumulation of nonfunctional "passenger" alterations that arise during repeated rounds of cell division in the tumor or in its progenitor stem cell. In light of the relatively low rates of mutation in human cancer cells (*9*, *10*), a distinction between selected and passenger mutations is generally not required when the number of genes and tumors analyzed is small. In large-scale studies, however, such distinctions are of paramount importance (*11*, *12*). For example, it has been estimated that nonsynonymous passenger mutations are present at a frequency no higher than ~1.2 per Mb of DNA in cancers of the breast or colon (*13*–*15*). Because we assessed 542 Mb of tumor DNA, we would therefore have expected to observe ~650 passenger mutations. We actually observed 1672 mutations (Table 1), many more than what would have been predicted to occur by chance ($P < 1 \times 10^{-10}$) (*7*). Moreover, the frequency of mutations in the validation screen was significantly higher than in the discovery screen (5.8 versus 3.1 mutations per Mb, $P < 1 \times 10^{-10}$; Table 1). The mutations in the validation screen were also enriched for nonsense, insertion, deletion, duplication, and splice site changes relative to the discovery screen; each of these would be expected to have a functional effect on the encoded proteins.

To distinguish genes likely to contribute to tumorigenesis from those in which passenger mutations occurred by chance, we first excluded genes that were not mutated in the validation screen. We next developed statistical methods to estimate the probability that the number of mutations in a given gene was greater than expected from the background mutation rate. For each gene, this analysis incorporated the number of somatic alterations observed in either the discovery or validation screens, the number of tumors studied, and the number of nucleotides successfully analyzed (as indicated by the number of bases with Phred quality scores of ≥20). Because the mutation frequencies varied with nucleotide type and context and were different in breast versus colorectal cancers (Table 2), these factors were included in the calculations. The output of this analysis was a cancer mutation prevalence (CaMP) score for each gene analyzed. The CaMP score reflects the probability that the number of mutations observed in a gene reflects a mutation frequency that is higher than that expected to be observed by chance given the background mutation rate; its derivation is based on principles described in (*7*). The use of the CaMP score for analysis of somatic mutations is analogous to the use of the lod score for linkage analysis in familial genetic settings. For example, 90% of the genes with CaMP scores of >1.0 are predicted to have mutation frequencies higher than the background mutation frequency.

Candidate cancer genes. A complete list of the somatic mutations identified in this study is provided in table S4. Validated genes with CaMP scores greater than 1.0 were considered to be candidate cancer genes (*CAN* genes). The combination of experimental validation and statistical calculation thereby yielded four nested sets of genes: Of 13,023 genes evaluated, 1149 were mutated, 236 were validated, and 189 were *CAN* genes. Among these, the *CAN* genes were most likely to have been subjected to mutational selection during tumorigenesis. There were 122 and 69 *CAN* genes identified in breast and colorectal cancers, respectively (tables S5 and S6). Individual breast cancers examined in the discovery screen harbored an average of 12 (range 4 to 23) mutant *CAN* genes, whereas the average number of *CAN* genes in colorectal cancers was 9 (range 3 to 18) (table S3). Interestingly, each cancer specimen of a given tumor type carried its own distinct *CAN*-gene mutational signature, as no cancer had more than six mutant *CAN* genes in common with any other cancer (tables S4 to S6).

CAN genes could be divided into three classes: (i) genes previously observed to be mutationally altered in human cancers, (ii) genes in which no previous mutations in human cancers had been discovered but had been linked to cancer through functional studies, and (iii) genes with no previous strong connections to neoplasia.

The reidentification of genes that had been previously shown to be somatically mutated in cancers represented a critical validation of the approach used in this study. All of the CCDS genes previously shown to be mutated in >10% of either breast or colorectal cancers were found to be *CAN* genes in the current study. These included *TP53* (*2*), *APC* (*2*), *KRAS* (*2*), *SMAD4* (*2*), and *FBXW7* (*CDC4*) (*16*) (tables S4 to S6). In addition, we identified mutations in genes whose mutation prevalence in sporadic cancers was rather low. These genes included *EPHA3* (*17*), *MRE11A* (*18*), *NF1* (*2*), *SMAD2* (*19*, *20*), *SMAD3* (*21*), *TCF7L2* (*TCF4*) (*22*), *BRCA1* (*2*), and *TGFBRII* (*23*). We also detected mutations in genes that had been previously found to be altered in human tumors but not in the same tumor type identified in this study. These included *GNAS* (guanine nucleotide binding protein, α stimulating) (*24*), *KEAP1* (kelch-like ECH-associated protein) (*25*), *RET* (a proto-oncogene) (*2*), and *TCF1* (a transcription factor) (*26*). Finally, we found mutations in a number of genes that have been previously identified as targets of translocation or amplification in human cancers. These included *NUP214* (a nucleoporin) (*2*), *KTN1* (a kinesin receptor) (*27*), *DDX10* (DEAD box polypeptide 10) (*28*), *GLI1* (glioma-associated oncogene homolog 1) (*29*), and *MTG8* (the translocation target gene of runt-related transcription factor 1, *RUNX1T1*) (*2*). We conclude that if these genes had not already been shown to play a causative role in human tumors, they would have been discovered through the approach taken in this study. By analogy, the 167 other *CAN* genes in tables S5 and S6 are likely to

Table 1. Summary of somatic mutations. Numbers in parentheses refer to percentage of total mutations.

Tumor	Discovery screen*			Validation screen†			Both screens combined		
	Colorectal	Breast	Total	Colorectal	Breast	Total	Colorectal	Breast	Total
Number of mutated genes	519	673	1149	105	137	236	519	673	1149
Number of mutations	574	733	1307	177	188	365	751	921	1672
Nonsynonymous mutations in coding sequences									
Missense	482 (84.0)	600 (81.9)	1082 (82.8)	126 (71.2)	145 (77.1)	271 (74.2)	608 (81.0)	745 (80.9)	1353 (80.9)
Nonsense	35 (6.1)	39 (5.3)	74 (5.7)	26 (14.7)	8 (4.3)	34 (9.3)	61 (8.1)	47 (5.1)	108 (6.5)
Insertion	3 (0.5)	3 (0.4)	6 (0.5)	2 (1.1)	2 (1.1)	4 (1.1)	5 (0.7)	5 (0.5)	10 (0.6)
Deletion	18 (3.1)	48 (6.5)	66 (5.0)	10 (5.6)	13 (6.9)	23 (6.3)	28 (3.7)	61 (6.6)	89 (5.3)
Duplication	17 (3.0)	2 (0.3)	19 (1.5)	3 (1.7)	12 (6.4)	15 (4.1)	20 (2.7)	14 (1.5)	34 (2.0)
Mutations in noncoding sequences									
Splice site‡	17 (3.0)	37 (5.0)	54 (4.1)	9 (5.1)	8 (4.3)	17 (4.7)	26 (3.5)	45 (4.9)	71 (4.2)
UTR§	2 (0.3)	4 (0.5)	6 (0.5)	1 (0.6)	0 (0.0)	1 (0.3)	3 (0.4)	4 (0.4)	7 (0.4)
Nucleotides successfully analyzed (Mb)‖	208.5	209.2	417.7	28.7	34.3	63.0	237.2	243.5	480.7
Mutation frequency (mutations/Mb)	2.8	3.5	3.1	6.2	5.5	5.8	3.2	3.8	3.5

*Coding and adjacent noncoding regions of 13,023 CCDS genes were sequenced in 11 colorectal and 11 breast cancers. †Genes mutated in the discovery screen were sequenced in 24 additional tumor samples of the affected tumor type. ‡Intronic mutations within 4 bp of exon/intron boundary. §Mutations in untranslated regions (UTR) within 4 bp 5′ of initiation codon or 4 bp 3′ of termination codon. ‖Nucleotides with Phred quality score of at least 20.

play important roles in breast, colorectal, and perhaps other types of cancers.

Although genetic alterations currently provide the most reliable indicator of a gene's importance in human neoplasia (*1*, *30*), many other genes are thought to play key roles on the basis of functional or expression studies. Our study provides genetic evidence supporting the importance of several of these genes in neoplasia. For example, we discovered intragenic mutations in *EPHB6* (an ephrin receptor) (*31*), *MLL3* (mixed-lineage leukemia 3) (*32*), *GSN* (gelsolin) (*33*), *CDH10* and *CDH20* (cadherins), *FLNB* (actin and SMAD binding protein filamin B) (*34*), *PTPRD* (protein tyrosine phosphatase receptor) (*35*), and *AMFR* (autocrine motility factor receptor) (*36*).

In addition to these two classes of genes, our study revealed a large number of genes that had not been strongly suspected to be involved in cancer. This third class of genes included *PKHD1* (polycystic kidney and hepatic disease 1), *GUCY1A2* (guanylate cyclase 1), *TBX22* (a transcription factor), *SEC8L1* (an exocyst complex component), *TTLL3* (a tubulin tyrosine ligase), *ATP8B1* (an ATP-dependent transporter), *CUBN* (an intrinsic factor-cobalamin receptor), *DBN1* (an actin binding protein), and *TECTA* (tectorin α). In addition, seven *CAN* genes corresponded to genes for which no biologic role has yet been established.

We examined the distribution of mutations within *CAN*-gene products to see whether clustering occurred in specific regions or functional domains. In addition to the well-documented hotspots in *TP53* (*37*) and *KRAS* (*38*), we identified three mutations in *GNAS* in colorectal cancers that affected a single amino acid residue (Arg^{201}). Alterations of this residue have previously been shown to lead to constitutive activation of the encoded heterotrimeric guanine nucleotide–binding protein (G protein) α_s through inhibition of guanosine triphosphatase (GTPase) activity (*24*). Two mutations in the EGF-like gene *EGFL6* in breast tumors affected the same nucleotide position and resulted in a $Leu^{508} \rightarrow$ Phe change in the MAM adhesion domain. A total of seven genes had alterations located within five amino acid residues of each other, and an additional 12 genes had clustering of multiple mutations within a specific protein domain (13 to 78 amino acids apart). Thirty-one of 40 of these changes affected residues that were evolutionarily conserved. Although the effects of these alterations are unknown, their clustering suggests specific roles for the mutated regions in the neoplastic process.

***CAN*-gene groups.** An unbiased screen of a large set of genes can provide insights into pathogenesis that would not be apparent through single-gene mutational analysis. This has been exemplified by large-scale mutagenesis screens in experimental organisms (*39*–*41*). We therefore attempted to assign each *CAN* gene to a functional group based on Gene Ontology (GO) molecular function or biochemical process groups, the presence of specific INTERPRO sequence domains, or previously published literature (Table 3 and Fig. 2). Several of the groups identified in this way were of special interest. For example, 22 of the 122 (18%) breast *CAN* genes and 13 of the 69 (19%) colorectal *CAN* genes were transcriptional regulators. At least one of these genes was mutated in more than 80% of the tumors of each type. Zinc-finger transcription factors were particularly highly represented (eight genes mutated collectively in 43% of breast cancer samples). Similarly, genes involved in cell adhesion represented ~22% of *CAN* genes and affected more than two-thirds of tumors of either type. Genes involved in signal transduction represented ~23% of *CAN* genes, and at least one such gene was mutated in 77% and 94% of the breast and colorectal cancer samples, respectively. Subsets of these groups were also of interest and included metalloproteinases (part of the cell adhesion and motility group and mutated in 37% of colorectal cancers) and G proteins and their regulators (part of the signal transduction group and altered in 43% of breast cancers). These data suggest that dysregulation of specific cellular processes is genetically selected during neoplasia and that distinct members of each group may serve similar roles in different tumors.

Discussion. Four important points have emerged from this comprehensive mutational analysis of human cancer. First, a relatively large number of previously uncharacterized *CAN* genes exist in breast and colorectal cancers, and these genes can be discovered by unbiased approaches such as that used in our study. These results support the notion that large-scale mutational analyses of other tumor types will prove useful for identifying genes not previously known to be linked to human cancer.

Second, our results suggest that the number of mutational events occurring during the evolution of human tumors from a benign to a metastatic state is much larger than previously thought. We found that breast and colorectal cancers harbor an average of 52 and 67 nonsynonymous somatic mutations in CCDS genes, of which an average of 9 and 12, respectively, were in *CAN* genes (table S3). These data can be used to estimate the total number of nonsynonymous mutations in coding genes that arise in a "typical" cancer through sequential rounds of mutation and selection. If we assume that the mutation prevalence in genes that have not yet been sequenced is similar to that of the genes so far analyzed, we estimate that there are 81 and 105 mutant genes (average 93) in the typical colorectal or breast cancer, respectively (*7*). Of these, an average of 14 and 20, respectively, would be expected to be *CAN* genes. In addition to the *CAN* genes, there were other mutated CCDS genes that were likely to have been selected for during tumorigenesis but were not altered at a frequency high enough to warrant confidence in their interpretation.

A third point emerging from our study is that breast and colorectal cancers show substantial differences in their mutation spectra. In colorectal cancers, a bias toward C:G to T:A transitions at 5′-CpG-3′ sites was previously noted in *TP53* (*42*). Our results suggest that this bias is genome-wide

Table 2. Spectrum of single base substitutions. Base substitutions in coding sequences resulting in nonsynonymous changes as well as substitutions in noncoding sequences are included (see Table 1). Numbers in parentheses indicate percentage of total mutations.

Tumor	Discovery screen			Validation screen			Both screens combined		
	Colorectal	Breast	Total	Colorectal	Breast	Total	Colorectal	Breast	Total
Total number of substitutions	535	678	1213	161	160	321	696	838	1534
Substitutions at C:G base pairs									
C:G → T:A	325 (60.7)	230 (33.9)	555 (45.8)	88 (54.7)	59 (36.9)	147 (45.8)	413* (59.3)	289* (34.5)	702 (45.8)
C:G → G:C	36 (6.7)	207 (30.5)	243 (20.0)	12 (7.5)	32 (20.0)	44 (13.7)	48* (6.9)	239* (28.5)	287 (18.7)
C:G → A:T	70 (13.1)	110 (16.2)	180 (14.8)	23 (14.3)	38 (23.8)	61 (19.0)	93 (13.4)	148 (17.7)	241 (15.7)
Substitutions at T:A base pairs									
T:A → C:G	42 (7.9)	54 (8.0)	96 (7.9)	14 (8.7)	18 (11.3)	32 (10.0)	56 (8.0)	72 (8.6)	128 (8.3)
T:A → G:C	38 (7.1)	30 (4.4)	68 (5.6)	13 (8.1)	5 (3.1)	18 (5.6)	51 (7.3)	35 (4.2)	86 (5.6)
T:A → A:T	24 (4.5)	47 (6.9)	71 (5.9)	11 (6.8)	8 (5.0)	19 (5.9)	35 (5.0)	55 (6.6)	90 (5.9)
Substitutions at specific dinucleotides†									
5′-CpG-3′	254 (47.5)	115 (17.0)	369 (30.4)	55 (34.2)	24 (15.0)	79 (24.6)	309* (44.4)	139* (16.6)	448 (29.2)
5′-TpC-3′	54 (10.1)	235 (34.7)	289 (23.8)	25 (15.5)	22 (13.8)	47 (14.6)	79* (11.4)	257* (30.7)	336 (21.9)

*Values in this category were significantly different between breast and colorectal cancers ($P < 0.0001$). †Includes substitutions at the C or G of the 5′-CpG-3′ dinucleotide, the C of the 5′- TpC-3′ dinucleotide, or the G of the 5′-GpA-3′ dinucleotide.

rather than representing a selection for certain nucleotides within *TP53*. This bias may reflect a more extensive methylation of 5′-CpG-3′ dinucleotides in colorectal cancers than in breast cancers, or it may be an effect of dietary carcinogens (*43*, *44*). In breast cancers, the fraction of mutations at 5′-TpC-3′ sites was far higher in the CCDS genes examined in this study than previously reported for *TP53* (*37*). It has been noted that a small fraction of breast tumors may have a defective repair system, resulting in 5′-TpC-3′ mutations (*15*). Our studies confirm that some breast

Table 3. Functional classification of *CAN* genes, with CaMP score to the right of each gene name. *CAN* genes were assigned to functional classes using Gene Ontology (GO) groups, INTERPRO domains, and available literature. Representative GO groups and INTERPRO domains are listed for each class.

Breast cancers						Colorectal cancers			
Cellular adhesion and motility (examples: cytoskeletal protein binding GO:0008092, cell adhesion GO:0007155, metallopeptidase activity GO:0008237)									
FLNB	3.4	*TMPRSS6*	2.0	*RAPH1*	1.4	*PKHD1*	3.5	*CNTN4*	1.6
MYH1	2.7	*COL11A1*	1.8	*PCDHB15*	1.4	*ADAMTSL3*	3.3	*CHL1*	1.3
SPTAN1	2.6	*DNAH9*	1.7	*CMYA1*	1.4	*OBSCN*	3.0	*HAPLN1*	1.2
DBN1	2.5	*OBSCN*	1.7	*MACF1*	1.3	*ADAMTS18*	2.7	*MGC33407*	1.2
TECTA	2.4	*COL7A1*	1.5	*SYNE2*	1.3	*MMP2*	2.3	*MAP2*	1.0
ADAM12	2.3	*MAGEE1*	1.5	*NRCAM*	1.1	*TTLL3*	2.2		
GSN	2.2	*CDH10*	1.5	*COL19A1*	1.1	*EVL*	2.0		
CDH20	2.2	*SULF2*	1.5	*SEMA5B*	1.1	*ADAM29*	2.0		
BGN	2.1	*CNTN6*	1.4	*ITGA9*	1.1	*CSMD3*	1.9		
ICAM5	2.1	*THBS3*	1.4			*ADAMTS15*	1.8		
Signal transduction (examples: intracellular signaling cascade GO:0007242, receptor activity GO:0004872, GTPase regulator GO:0030695)									
VEPH1	2.1	*PFC*	1.5	*PRPF4B*	1.3	*APC*	>10	*PTPRD*	2.2
SBNO1	2.1	*GAB1*	1.5	*CENTG1*	1.3	*KRAS*	>10	*MCP*	2.1
DNASE1L3	1.9	*ARHGEF4*	1.4	*MAP3K6*	1.3	*EPHA3*	4.2	*NF1*	1.9
RAP1GA1	1.8	*NALP8*	1.4	*APC2*	1.3	*GUCY1A2*	3.5	*PTPRU*	1.4
EGFL6	1.8	*RGL1*	1.4	*STARD8*	1.2	*EPHB6*	3.5	*CD109*	1.3
AMFR	1.7	*PPM1E*	1.4	*PTPN14*	1.1	*TGFBR2*	2.9	*PHIP*	1.2
CENTB1	1.7	*PKDREJ*	1.4	*IRTA2*	1.1	*GNAS*	2.6		
GPNMB	1.7	*CNNM4*	1.3	*RASGRF2*	1.1	*RET*	2.3		
INHBE	1.7	*ALS2CL*	1.3	*MTMR3*	1.1	*P2RY14*	2.2		
FLJ10458	L.6	*RASAL2*	1.3			*LGR6*	2.2		
Transcriptional regulation (examples: regulation of transcription GO:0045449, zinc finger C2H2-subtype IPR007066)									
TP53	>10	*CHD5*	1.8	*ZFP64*	1.4	*TP53*	>10	*ZNF442*	1.9
FLJ13479	3.4	*CIC*	1.7	*ZNF569*	1.4	*SMAD4*	4.6	*SMAD3*	1.9
SIX4	2.5	*KEAP1*	1.6	*EHMT1*	1.3	*MLL3*	3.7	*EYA4*	1.5
KIAAO934	2.5	*HOXA3*	1.6	*ZFYVE26*	1.2	*TBX22*	3.3	*PKNOX1*	1.4
LRRFIP1	2.4	*TCF1*	1.6	*BCL11A*	1.1	*SMAD2*	3.1	*MKRN3*	1.3
GLI1	2.3	*HDAC4*	1.6	*ZNF318*	1.1	*TCF7L2*	2.8		
RFX2	2.1	*MYOD1*	1.5			*HIST1H1B*	2.5		
ZCSL3	1.8	*NCOA6*	1.5			*RUNX1T1*	2.4		
Transport (examples: ion transporter activity GO:0015075, ligand-gated ion channel activity GO:0015276, carrier activity GO:0005386)									
ATP8B1	3.1	*ABCB8*	1.7	*ABCB10*	1.4	*ABCA1*	2.8	*C6orf29*	1.1
CUBN	2.5	*KPNA5*	1.7	*SCNN1B*	1.3	*SLC29A1*	1.9		
GRIN2D	2.4	*ABCA3*	1.7	*NUP133*	1.1	*SCN3B*	1.9		
HDLBP	2.2	*SLC9A2*	1.6			*P2RX7*	1.3		
NUP214	1.8	*SLC6A3*	1.5			*KCNQ5*	1.2		
Cellular metabolism (examples: aromatic compound metabolism GO:0006725, generation of precursor metabolites GO:0016445. biosynthesis GO:0009058)									
ACADM	2.0	*NCB50R*	1.7	*PHACS*	1.4	*UQCRC2*	1.9		
PRPS1	1.8	*ASL*	1.6	*XDH*	1.3	*ACSL5*	1.6		
CYP1A1	1.7	*GALNT5*	1.4			*GALNS*	1.2		
Intracellular trafficking (examples: endoplasmic reticulum targeting sequence IPR000866, membrane fusion GO:0006944)									
OTOF	2.2	*PLEKHA8*	1.8	*KTN1*	1.5	*SYNE1*	2.3	*PRKD1*	1.9
LRBA	2.1	*LOC283849*	1.7	*GGA1*	1.4	*SEC8L1*	2.2	*LRP2*	1.2
AEGP	1.8	*SORL1*	1.7			*SDBCAG84*	2.2		
RNA metabolism (examples: RNA processing GO:0008353, RNA splice site selection GO:0006376)									
C14orf155	3.3	*RNU31P2*	1.7	*KIAA0427*	1.5	*SFRS6*	1.3		
SP110	1.8	*C22orfl9*	1.5	*DDX10*	1.3				
Other (examples: response to DNA damage stimulus GO:0006974, protein ubiquitination GO:0016567)									
FLJ40869	2.1	*SERPINB1*	1.4			*FBXW7*	5.1	*K6IRS3*	1.2
BRCA1	2.0					*UHRF2*	1.5	*CD248*	1.2
MRE11A	1.6					*LMO7*	1.3	*ERCC6*	1.0
Unknown									
KIAA1632	2.4	*KIAA0999*	1.3			*C10orf137*	2.7	*KIAA1409*	1.6
MGC24047	2.1					*LOC157697*	2.0	*C15orf2*	1.0

cancers have higher fractions of 5′-TpC-3′ mutations than others, but also show that mutations at this dinucleotide are generally more frequent than in colorectal cancers (Table 2 and table S3).

Finally, our results reveal that there are substantial differences in the panel of *CAN* genes mutated in the two tumor types (Table 3). For example, metalloproteinase genes were mutated in a large fraction of colorectal but only in a small fraction of breast cancers (tables S5 and S6). Transcriptional regulator genes were mutated in a high fraction of both breast and colorectal tumors, but the specific genes affected varied according to tumor type (Table 3). There was also considerable heterogeneity among the *CAN* genes mutated in different tumor specimens derived from the same tissue type (tables S4 to S6). It has been documented that virtually all biochemical, biological, and clinical attributes are heterogeneous within human cancers of the same histologic subtype (*45*). Our data suggest that differences in the genes mutated in various tumors could account for a major part of this heterogeneity. This might explain why it has been so difficult to correlate the behavior, prognosis, or response to therapy of common solid tumors with the presence or absence of a single gene alteration; such alterations reflect only a small component of each tumor's mutational composition. On the other hand, disparate genes contributing to cancer are often functionally equivalent, affecting net cell growth through the same molecular pathway (*1*). Thus, *TP53* and *MDM2* mutations exert comparable effects on cells, as do mutations in *RB1*, *CDKN2A* (*p16*), *CCND1*, and *CDK4*. It will be of interest to determine whether a limited number of pathways include most *CAN* genes, a possibility consistent with the groupings in Fig. 2 and Table 3.

Like a draft version of any genome project, our study has limitations. First, only genes present in the current version of CCDS were analyzed; of the genes not yet included, there are ~5000 genes for which excellent supporting evidence exists (*46*). Second, we were not able to successfully sequence ~10% of the bases within the coding sequences of the 13,023 CCDS genes (equivalent to 1302 unsequenced genes). Third, our identification of genes mutated at significant frequencies assumed that the background mutation frequency was constant throughout the genome. Although it cannot currently be determined whether certain genomic regions have higher background mutation frequencies, we have included the number of mutations observed per Mb sequenced in tables S5 and S6 to facilitate such analyses in the future. Fourth, although our screen would be expected to identify the most common types of mutations found in cancers, some genetic alterations—including mutations in noncoding genes, mutations in noncoding regions of coding genes, relatively large deletions or insertions, amplifications, and translocations—would not be detectable by the methods we used. Future studies using a combination of different technologies, such as those envisioned by the Cancer Genome Atlas Project (*47*), will be able to address these issues.

The results of this study inform future cancer genome sequencing efforts in several important ways:

1) A major technical challenge of such studies will be discerning somatic mutations from the large number of sequence alterations identified. In our study, 557,029 nonsynonymous sequence alterations were detected in the discovery screen, but after subsequent analyses only 0.23% of these were identified as legitimate somatic mutations (Fig. 1). Fewer than 10% of the putative nonsynonymous alterations were known polymorphisms; many of the rest were uncommon germline variants or sequence artifacts that were not reproducible. Inclusion of matched normal samples and sequencing both strands of each PCR product would reduce false positives in the discovery screen but would increase the cost of sequencing by a factor of 4. Although recently developed sequencing methods could reduce the cost of such studies in the future (*48*), the higher error rates of these approaches may result in an even lower ratio of bona fide somatic mutations to putative alterations.

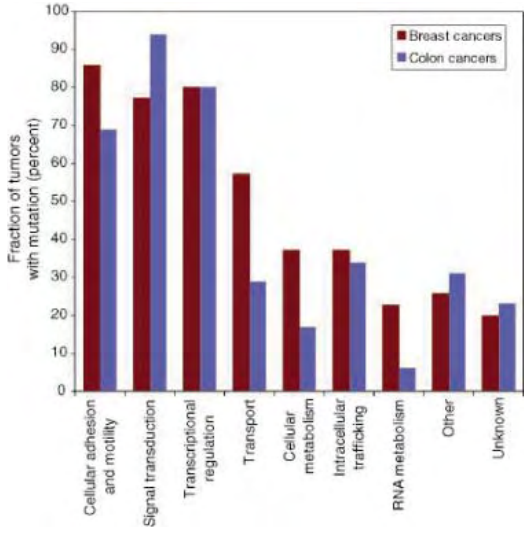

Fig. 2. Mutation frequency of *CAN*-gene groups. *CAN* genes were grouped by function with the use of Gene Ontology groups, INTERPRO domains, and available literature. Bars indicate the fraction of tumors (35 breast or 35 colorectal) with at least one mutated gene in the functional group.

2) Another technical issue is that careful design of primers is important to eliminate sequence artifacts due to the inadvertent amplification and sequencing of related genes. The primer pairs that resulted in successful amplification and sequencing represent a valuable resource in this regard. Even with well-designed primers, it is essential to examine any observed mutation to ensure that it is not found as a normal variant in a related gene.

3) Although it is likely that studies of other solid tumor types will also identify a large number of somatic mutations, it will be important to apply rigorous approaches to identify those mutations that have been selected for during tumorigenesis. Statistical techniques, such as those used in this study or described by Greenman *et al*. (*11*), can provide strong evidence for selection of mutated genes. These approaches are likely to improve as more cancer genomic sequencing data are accumulated through the Cancer Genome Atlas Project (*47*) and other projects now under way.

4) There has been much discussion about which genes should be the focus of future sequencing efforts. Our results suggest that many genes not previously implicated in cancer are mutated at significant levels and may provide novel clues to pathogenesis. From these data, it would seem that large-scale unbiased screens of coding genes may be more informative than screens based on previously defined criteria.

5) The results also raise questions about the optimum number of tumors of any given type that should be assessed in a cancer genome study. Our study was designed to determine the nature and types of alterations present in an "average" breast or colorectal cancer and to discover genes mutated at reasonably high frequencies. With this design, our power to detect genes mutated in more than 20% of tumors of a given type was 90%, but only 50% of genes mutated in 6% of tumors would have been discovered. Detection of genes mutated in 6% or 1% of tumors with >99% probability in a discovery screen would require sequence determination of at least 75 or 459 tumors, respectively. Although it will be impossible to detect all mutations that may occur in tumors, strategies that would identify the most important ones at an affordable cost can be envisioned on the basis of the data and analysis reported herein.

6) Ultimately, the sequences of entire cancer genomes, including intergenic regions, will be obtainable. Our studies demonstrate the inherent difficulties in determining the consequences of somatic mutations, even those that alter the amino acid sequence of highly annotated and well-studied genes. Establishing the consequences of mutations in noncoding regions of the genome will likely be much more difficult. Until new tools for solving this problem become available, it is likely that gene-centric sequencing analyses of cancer will be more useful than whole-genome sequencing.

Our results provide a large number of future research opportunities in human cancer. For genetics, it will be of interest to elucidate the timing

and extent of *CAN*-gene mutations in breast and colorectal cancers, whether these genes are mutated in other tumor types, and whether germline variants in *CAN* genes are associated with cancer predisposition. For immunology, the finding that tumors contain an average of ~90 different amino acid substitutions not present in any normal cell can provide novel approaches to engender antitumor immunity. For epidemiology, the remarkable difference in mutation spectra of breast and colorectal cancers suggests the existence of organ-specific carcinogens. For cancer biology, it is clear that no current animal or in vitro model of cancer recapitulates the genetic landscape of an actual human tumor. Understanding and capturing this landscape and its heterogeneity may provide models that more successfully mimic the human disease. For epigenetics, it is possible that a subset of *CAN* genes can also be dysregulated in tumors through changes in chromatin or DNA methylation rather than through mutation. For diagnostics, the *CAN* genes define a relatively small subset of genes that could prove useful as markers for neoplasia. Finally, some of these genes, particularly those on the cell surface or those with enzymatic activity, may prove to be good targets for therapeutic development.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/1133427/DC1
Materials and Methods
Figs. S1 and S2
Tables S1 to S5
References

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REPORTS

Self-Assembly of CdTe Nanocrystals into Free-Floating Sheets

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In their physical dimensions, surface chemistry, and degree of anisotropic interactions in solution, CdTe nanoparticles are similar to proteins. We experimentally observed their spontaneous, template-free organization into free-floating particulate sheets, which resemble the assembly of surface layer (S-layer) proteins. Computer simulation and concurrent experiments demonstrated that the dipole moment, small positive charge, and directional hydrophobic attraction are the driving forces for the self-organization process. The data presented here highlight the analogy of the solution behavior of the two vastly different classes of chemical structures.

Understanding the ability of nanoparticles (NPs) to self-assemble will influence both the fundamental picture of the properties of matter on the nanoscale and the practical realization of bottom-up fabrication technologies (*1*–*3*). Self-organization processes in solution have been well established for proteins and other biomacromolecules (*4*–*6*), which have physical dimensions of several nanometers, i.e., the same scale as that of many inorganic nanocolloids. Recent studies demonstrate nanoparticle self-organization into one-dimensional (1D) structures driven by anisotropic dipolar interparticle forces (*7*–*9*). Highly uniform nanocolloids, with presumably isotropic interactions, can form 3D arrays or crystals (*10*–*14*). Two-dimensional arrays of NPs produced at two-phase interfaces—such as gas-solid (*10*), liquid-solid (*15*), gas-liquid (*16*), or liquid-liquid (*17*)—where the interfaces act as a template, are well known. We report that the combination of the electrostatic interaction and anisotropic hydrophobic attraction between NPs with tetrahedral shape result in the spontaneous formation of 2D free-floating sheets. The sheets display considerable mechanical robustness and retain size-quantized properties of the semiconductor NP with characteristic luminescence. Notably, they do not require any interface that may give dimension-restrictive cues

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and form entirely due to specific NP-NP interactions, which changes the paradigm of self-organization processes for NPs.

2-(Dimethylamino)ethanethiol (DMAET)–stabilized CdTe NPs with positive charges were synthesized by the Rogach-Weller method (*18*, *19*). Transmission electron microscopy (TEM) (Fig. 1A) and tapping-mode atomic force microscopy (AFM) images (Fig. 1B) indicate the formation of objects that can be characterized as free-floating sheets formed by a 2D network of assembled NPs (Fig. 1C). In both TEM and AFM images, these sheets appear as flat, semifolded, and even wrinkled platelets. The semifolded structures demonstrate that the 2D NP sheets form in solution rather than on the substrate during drying. Using TEM, we estimate that more than 99% of the NPs assembled into sheets. We found similar sheets for CdSe NPs when we used the same stabilizer, which indicates the potential generality of the phenomenon (fig. S3).

The sheets possess some physical integrity, and some pieces as large as 50 μm by 30 μm (Fig. 1A) remain after gentle stirring and drying. The average AFM thickness of the NP sheets is 3.4 ± 0.2 nm (50 measurements). Because our DMAET-stabilized CdTe nanocrystals are 3.4 nm in diameter as determined by TEM, we conclude that the sheets are monolayers. A total height of 6.8 nm is found for smaller pieces spread atop larger ones and corresponds to the height of NP bilayers (Fig. 1B).

The NP sheets in solution have easily detectable photoluminescence (PL) with a quantum yield of 2.1%, which is considerably lower than the 30% quantum yield of the unassembled CdTe. The assembly also caused the PL peak to be red-shifted from 557 to 564 nm, i.e., by 27 meV (Fig. 2A). These observations are consistent with PL quenching due to excitation transfer in the closely spaced NP system also resulting in the preferential emission from larger NPs (*20*, *21*). Nevertheless, the optical activity is sufficiently high to obtain confocal microscopy images under ambient conditions (Fig. 2, C and D). The confocal images correlate well with the TEM and AFM micrographs. The green-yellow emission of the films is the same over the entire sheet regardless of size, and the corresponding PL image matches the optical image (Fig. 2, B and C), which reflects the equal degree of quantization of the NPs that form the free-floating film. In this size regime, the emission color of CdTe is extremely sensitive to changes in particle diameter. Thus, the particles retain the individuality of their semiconducting cores. The same conclusion can be reached with CdTe NPs of different diameters (from 2.4 to 5.0 nm) and with different PL wavelengths (Fig. 2D). Confocal images also indicate that the interparticle forces driving sheet formation do not involve recrystallization of the CdTe atomic structure as observed in the self-assembly of CdTe nanowires (*7*); otherwise, color variations would have been observed. Some intensity variations along the sheet surface reflect the presence of films with double thicknesses due to additional pieces picked up from the solution (Fig. 1, A and B).

What is the mechanism underlying the formation of free-floating NP sheets rather than traditional 3D agglomeration and precipitation? One hypothesis, that sheets form on the vessel walls, has been excluded after multiple blank experiments based on a variety of techniques (see supporting online material). The results of confocal optical microscopy (fig. S1), light-scattering data (fig. S2, A to E), and TEM of the intermediate state (fig. S2F) are consistent with this conclusion. Semiconductor nanocolloids with zinc blend atomic packing (Fig. 1C) were experimentally determined by several groups to have a dipole moment (*22*–*24*) contributing to the self-assembly of these particles into 1D chains and nanowires (*7*, *24*–*26*). Additionally, DMAET molecules confer some positive charge to the NPs, which we estimate to be 1 to 3*e* as in (*27*). There is also a strong hydrophobic attraction between the NPs, because DMAET has two hydrophobic methyl groups (*28*). We did not deplete the stabilizer layer by precipitating it with methanol (antisolvent), as our group had done previously with thioglycolic acid (*7*). This method maintains the individuality of the NP cores seen in the TEM images (Fig. 1, A and C).

On the basis of these observations and considering the relatively short length of the stabilizers (0.55 nm compared with the NP size of 2 to 5 nm), we conjecture that anisotropic electrostatic interactions arising from both a dipole moment and a small positive charge, combined with directional hydrophobic attraction, are responsible for the formation of the 2D free-floating films. Molecular simulations based on a coarse-grained model with proper parameters determined by semi-empirical quantum mechanics calculations were performed to validate the proposed hypothesis. The origin of the dipole moment in zinc-blend structured NPs is attributed to the truncation of the tetrahedrons (*22*, *24*, *29*). The high-energy apices of the tetrahedron are likely to be replaced with less energetic crystal planes in NPs (*1*, *30*). Some of the four apices may be truncated, and some of them may remain. For the molecular simulations, we start from a model NP with three truncated apices. For a NP of 2.53-nm width and 2.95-nm height (Fig. 3A), semi-empirical PM3 quantum mechanical calculations indicate that the CdTe NP has a dipole moment of 107.74 D when the truncated corners are coated with H_2O and 56.75 D when the truncated corners are coated with sulfhydryl (SH). These values are consistent with reported values of 50 to 100 D (*22*).

A coarse-grained "patchy particle" model proposed previously by Zhang and Glotzer is used to study the self-assembly of NPs with complex shape and anisotropic interactions, here by Monte Carlo (MC) simulations (*31*). Sixty-two beads were rigidly linked together into the shape of a truncated tetrahedron (Fig. 3B). The beads interact with a hard core

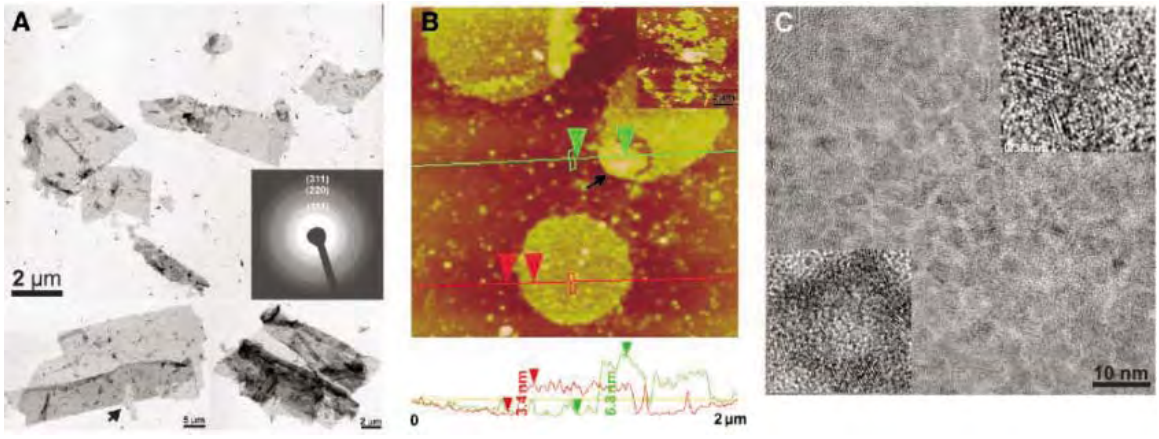


Fig. 1. (**A**) TEM images of free-floating films of CdTe NPs. (Inset) Electron diffraction pattern obtained from the films. (**B**) Tapping-mode AFM and corresponding topography cross sections of the monolayer films on a silica surface. (Inset) Large-scale AFM image of the films. The morphology of the films is the same for hydrophilic and hydrophobic TEM grids, as well as for AFM images obtained on hydrophilic and hydrophobic Si substrates. The drying of the dispersion, which is different on substrates with different wettabilities, is not a factor in the sheet formation. (**C**) High-resolution TEM (HRTEM) images of the monolayer films of CdTe NPs. The inset at top right represents a detailed arrangement of single NPs obtained by HRTEM. Each particle has a distinct cubic crystal structure identified from the spacing between adjacent crystal planes inside the NPs equal to 0.38 nm, which corresponds to (111) surfaces of zinc blend CdTe. Inset at bottom left shows characteristic assembled rings of cubic CdTe NPs with zinc blend cubic crystal structure. The error bars represent the standard deviation.

repulsive interaction to model the excluded volume effect between the NPs. The diameter of each bead is σ = 0.5 nm. The corresponding NP size is h = 2.86 nm and w = 2.50 nm, which is close to the size used in the quantum calculation in Fig. 3A. As mentioned previously, the stabilizer length is much smaller than the NP size; therefore, the hydrophobic attraction only exists between the pair faces and is short-ranged and directional. This is modeled by a square-well potential modulated by an angular term (Fig. 3C) (*32*)

$$U_{ij}(r_{ij};\mathbf{Q}_i,\mathbf{Q}_j) = u^{hssw}(r_{ij}) \cdot f(\mathbf{Q}_i,\mathbf{Q}_j) \quad (1)$$

where u^{hssw} is the regular hard sphere square-well potential

$$u^{hssw}(r_{ij}) = \begin{cases} \infty & \text{for } overlap \\ -\xi & \text{for } r_{ij} < 2l + \lambda,\ non-overlap \\ 0 & \text{for } r_{ij} \geq 2l + \lambda,\ non-overlap \end{cases} \quad (2)$$

Here ξ is the depth of the square-well potential related to the strength of the hydrophobic attraction, r_{ij} is the distance between the centers of mass of NP i and j, l is the distance from the mass center of the NP to the tetrahedron face, and λ is the interaction range. The function $f(\mathbf{Q}_i, \mathbf{Q}_j) = 1$ only if NPs i and j are oriented so that the angle between the vector joining their mass centers and the normal vector of the crystal face is less than δ; otherwise, $f(\mathbf{Q}_i, \mathbf{Q}_j) = 0$. The angle δ and interaction range λ in combination determine the directionality of the attraction between the faces of two NPs, which can be estimated by the length ratio of the stabilizer and NP. For example, the stabilizer length is ~0.55 nm and δ is ~18° (Fig. 3A). Thus, we chose λ = 0.55 nm and δ = 18° in the MC simulations (Fig. 3C). The electrostatic potential between two NPs U_{ij} is modeled by

$$U_{ij}(r_{ij}) = \frac{q_i q_j}{4\pi\varepsilon_0\varepsilon r_{ij}} e^{-kr_{ij}} C_0^2 + \frac{q_i\mu_j \cos\theta_j + q_j\mu_i \cos\theta_i}{4\pi\varepsilon_0\varepsilon r_{ij}^2} e^{-kr_{ij}} C_0 C_1 + \frac{\mu_i\mu_j}{4\pi\varepsilon_0\varepsilon r_{ij}^3}\left\{\cos\theta_i \cos\theta_j\left[2 + kr_{ij} + (kr_{ij})^2\right] + \sin\theta_i \sin\theta_j \cos(\phi_i - \phi_j)[1 + kr_{ij}]\right\} e^{-kr_{ij}} C_1^2 \quad (3)$$

which was proposed by Phillies for polyelectrolyte colloids and proteins in dilute solution (*33*).

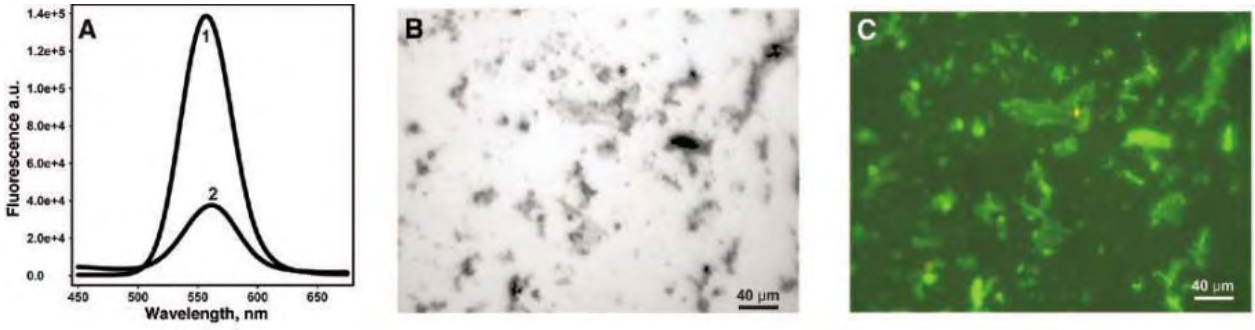
In the above equation, $C_0 = \frac{e^{ka}}{1+ka}$ and

$$C_1 = \frac{3e^{ka}}{2 + 2ka + (ka)^2 + \varepsilon_0(1+ka)/\varepsilon} \quad (4)$$

Here q_i and q_j are the net charge carried by NP i and NP j; μ_i and μ_j are dipole moments; r_{ij} is the distance between two NPs; θ_i and θ_j are angles of the dipole vector with respect to the vector connecting the centers of the NPs, where $0 < \theta < \pi$; φ_i and φ_j are dihedral angles describing the relative rotation of dipoles, where $0 < \varphi < 2\pi$; $1/k$ is the Debye screening length, which is set to be 2.5 nm; ε_0 is the permittivity of vacuum; ε is the effective permittivity of the solvent (water); and a is the radius of a NP. The dipole moment is set to be 100 D, as suggested

Table 1. Electrostatic energy of two NPs as a function of relative orientation (separation r = 0.55 nm). U_{qq}: charge-charge interaction; $U_{q\mu}$: charge-dipole interaction; $U_{\mu\mu}$: dipole-dipole interaction; U_t: total electrostatic interaction. All energy is in units of kJ/mol. Δφ is the dihedral angle between the dipole directions of neighboring NPs.

Relative orientation	Bottom-bottom	Bottom-side	Side-side			
			Δφ = 0°	Δφ = 60°	Δφ = 120°	Δφ = 180°
U_{qq}	53.47	53.47	53.47	53.47	53.47	53.47
$U_{q\mu}$	45.63	15.21	−15.21	−15.21	−15.21	−15.21
$U_{\mu\mu}$	12.40	−4.13	5.91	3.64	−0.89	−3.15
U_t	111.50	64.55	44.17	41.90	37.37	34.85



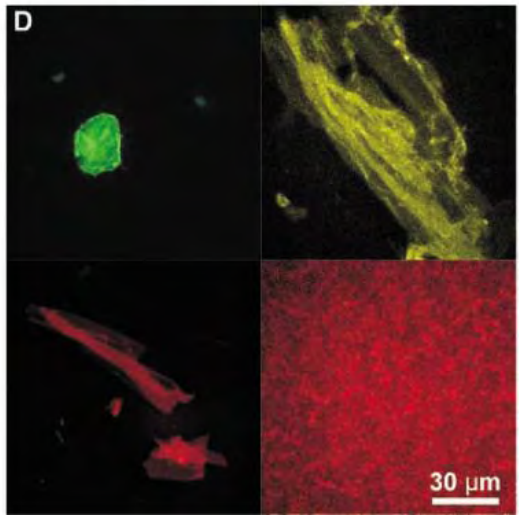


Fig. 2. (**A**) PL spectra of the solution of original CdTe NPs (1) and the dispersion of the free-floating NP films (2). Optical (**B**) and fluorescence (**C**) images of the self-assembled NP sheets. (**D**) Fluorescence images of self-assembled sheets of green-emitting NPs with a diameter of ~2.4 nm (top left), yellow-emitting NPs with a diameter of ~3.6 nm (top right), and red-emitting NPs with a diameter of ~5.0 nm (bottom left). The inset (bottom right) represents an analogous image of red-emitting NPs before self-assembly, demonstrating only disordered aggregation on glass substrates. The optical and fluorescent microscopy images were processed by Leica TCS NT confocal microscopy software. A 488-nm line of a water-cooled Ar-ion laser was used for luminescence excitation.

by our quantum calculations. The net charge q is set to be $+3e$ as determined by experimental measurements (*27*).

MC simulations in the canonical ensemble (constant number of NPs, volume, temperature) are performed in a cubic box with periodic boundary conditions implemented in all three Cartesian directions. A MC step is defined as N (number of NPs) attempts at moving the particles by either translation or rotation. The simulations begin from a disordered state that is obtained by running 3 to 5 million MC steps with attractive energy $\xi = 0.0$ and temperature $T = 25°C$. ξ is then gradually increased from a low value (disordered state) to a high value at which ordered films are formed. We investigated three different systems: $N = 20$ at volume fraction $\phi = 0.13$, $N = 30$ at $\phi = 0.12$, and $N = 60$ at $\phi = 0.13$. Twenty independent runs were performed for the first two systems and four independent runs were performed for the third system. All of them demonstrate that CdTe NPs self-assemble into 2D monolayer films in solution (Fig. 3, D and E). We did not observe sheet formation in simulation in the absence of either the dipole moment, the net positive charge, or the hydrophobic attraction. This point was also exhaustively confirmed experimentally by varying the surface charge, ionic strength, stabilizer length, and the NP material (figs. S3 to S9). For instance, Au NPs with a very small dipole moment do not form the sheets, whereas similar CdSe NPs do. Simulated structures for these cases also match the experimental observations well (figs. S5, S7, and S11).

The simulation results further reveal that the basic units in each 2D monolayer are rings composed of six NPs, in which every bottom-upward NP is adjacent to three corner-upward NPs, and vice versa (Fig. 3E). The ring structures can also be seen in high-resolution TEM images of CdTe NP sheets (Fig. 1C, inset). The large-scale ordering in this system is difficult to discern (Fig. 1C). This is due to variations of NP diameter, geometry, truncations, and stabilizer distribution, which are inevitable for NPs produced in aqueous solutions with a relatively short stabilizer.

It is convenient to introduce the order parameter $S = (\frac{3}{2}\mathbf{S} : \mathbf{S})^{1/2}$ in which $\mathbf{S}$ is the orientational tensor defined by $\mathbf{S} = \langle \boldsymbol{uu} \rangle - \frac{1}{3}\mathbf{e}$, where $\mathbf{u}$ is the unit vector of the dipole moment and $\mathbf{e}$ is the unit tensor, to describe the organization of the NP system, as used for liquid crystals. Ordering in the system should depend on the strength of the specific interactions. Indeed, there is a transition in the order parameter S at $\xi = 58$ to 59.5 kJ/mol as the attraction increases (Fig. 3F), which is similar for different systems (fig. S10). Simulations of larger systems confirmed the stability of the sheets (see supporting online material).

We also evaluate the potential energy between two NPs as a function of relative orientation to elucidate how the locally anisotropic interactions conspire to produce a global symmetry-broken 2D structure. The truncated tetrahedral shape of the NP causes the hydrophobic attraction between them to be anisotropic, i.e., the bottom-bottom, bottom-side, and side-side alignments are favored. The energy of attraction remains the same (square-well interaction) in all of these orientations, whereas the energy of electrostatic interactions does not (Table 1). The combined lowest energy state is the side-side orientation with opposite dipole directions ($\Delta\varphi = 180°$), which we indeed find in the simulations. The energy difference between the lowest energy state (side-side, $\Delta\varphi = 180°$) and the next lowest energy state (side-side, $\Delta\varphi =$

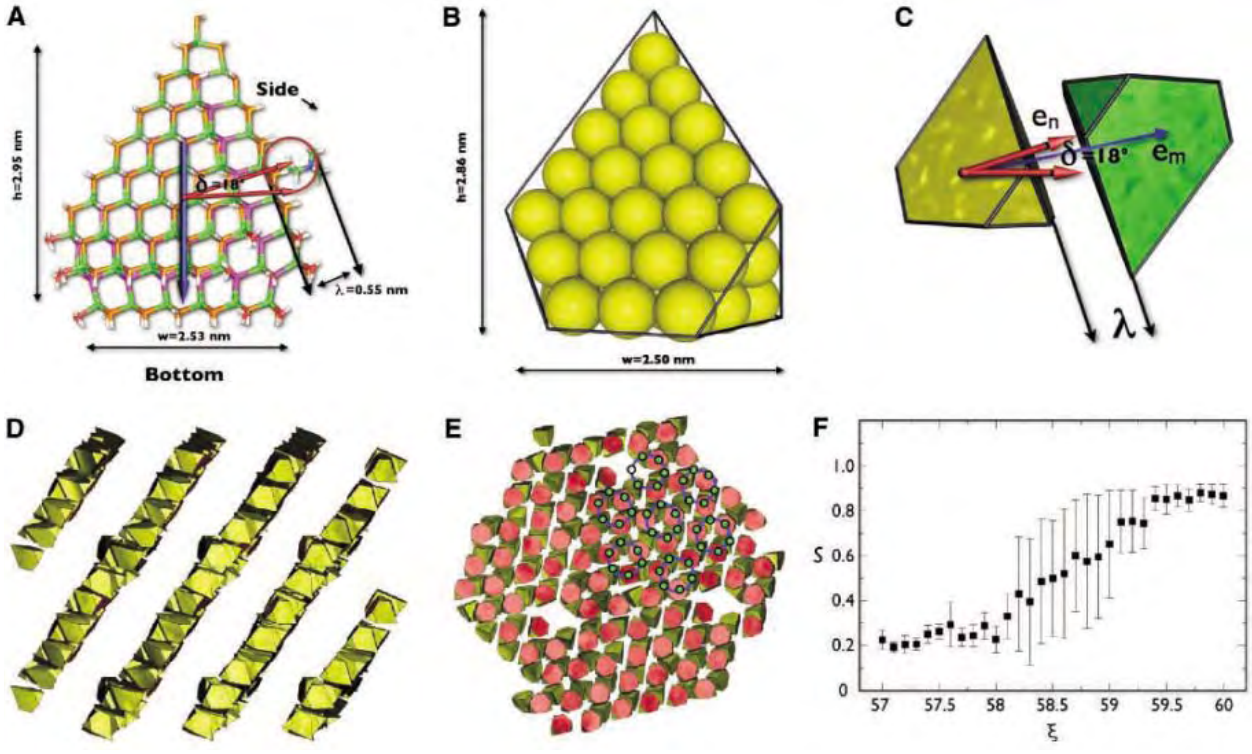


Fig. 3. Computer simulations of self-assembly of CdTe NPs. (**A**) Semi-empirical PM3 quantum calculation of a single CdTe NP by Spartan V4. Colors: Cd (green), Te (purple), S (orange), O (red), and H (white). The surface of the NP is coated by SH groups as a minimal model of the DMAET stabilizers. The stabilizers attached to the truncated corners are either SH or water molecules. The angle δ, which determines the directionality of hydrophobic attraction between faces, is ~18°. The calculated dipole direction is illustrated by the blue arrow. Its negative direction points toward the bottom of the crystal. (**B**) Coarse-grained model of a single NP made from 62 beads of uniform size. (**C**) Schematic illustration of the model for the directional hydrophobic attraction between NPs. $\mathbf{e}_n$ is the normal vector of the faces; $\mathbf{e}_m$ is the vector connecting the mass centers of NPs. Two NPs are attractive only when the angle between $\mathbf{e}_n$ and $\mathbf{e}_m$ is less than $\delta = 18°$. (**D**) Side view of films obtained by mesoscale simulation with $N = 480$ and $\phi = 0.13$. The system size shown here has been doubled for clarity. (**E**) Face view of a single sheet in (D). The basic structure within the sheet is rings composed of six NPs, indicated by dotted circles. (**F**) The dependence of the scalar order parameter, S, as a function of ξ as obtained by an average over four independent runs ($N = 60$ and $\phi = 0.13$). The error bars represent the standard deviation.

120°) is 2.52 kJ/mol, which is comparable with the energy of thermal noise. Table 1 also demonstrates the necessity of a small positive charge in addition to the dipole moment to form sheets. Without net charge the lowest energy state is the bottom-side orientation, preventing the formation of 2D monolayers (fig. S11).

Using the same modeling strategy, one can consider NPs with different numbers of corners truncated. NPs with zero or one truncated corners cannot form 2D monolayers due to the steric constraints between the untruncated corners of adjacent NPs. NPs with two truncated corners form chains instead of monolayers (fig. S12). Although 2D self-assembly was observed only for NPs with three truncated corners, we do not exclude the existence of NPs with other number of truncated corners in the experimentally obtained sheets, including those with four truncated corners, because the net dipole moment inside those NPs can be induced by other adjacent NPs (*24*). The inclusions will show up as defects within the sheet (Fig. 1C). Nevertheless, the arrangement of NPs with three adjacent NPs in a 2D film is the most energetically favorable.

The interactions between NPs in general are complex and diverse, which offers tremendous opportunities for the design of NP assemblies with varying shapes, structures, and functions (*31*, *34*). This study of 2D self-assembly of NPs demonstrates (i) the importance of anisotropy of interparticle interactions at the nanoscale and (ii) methods for the manipulation and prediction of spontaneous NP assemblies. These data also show a surprising resemblance of NPs to self-ordering biological systems, such as S-layer–forming proteins (*4*–*6*). This is particularly important for establishing correlations between protein superstructures and inorganic nanostructures on the basis of their similar sizes.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5797/274/DC1
Materials and Methods
Figs. S1 to S12

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Dynamic Stark Control of Photochemical Processes

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A method is presented for controlling the outcome of photochemical reactions by using the dynamic Stark effect due to a strong, nonresonant infrared field. The application of a precisely timed infrared laser pulse reversibly modifies potential energy barriers during a chemical reaction without inducing any real electronic transitions. Dynamic Stark control (DSC) is experimentally demonstrated for a nonadiabatic photochemical reaction, showing substantial modification of reaction channel probabilities in the dissociation of IBr. The DSC process is nonperturbative and insensitive to laser frequency and affects all polarizable molecules, suggesting broad applicability.

Molecular catalysts increase chemical reaction rates by applying forces that modify potential energy barriers along a reaction coordinate. Because electrical forces underlie all of chemistry, such barrier manipulation is also possible by application of a laser field. The duration of modern ultrafast laser pulses is on the time scale of chemistry itself, and therefore precise control over the form and delay of these pulses offers access to different portions of a potential energy surface as a reaction occurs. DSC is a technique that uses nonresonant infrared laser fields to dynamically alter a potential energy landscape during a photochemical reaction. The application of this field modifies the potential surface via the Stark effect, enhancing or inhibiting a specific reaction channel. Importantly, it does so without inducing any real electronic transitions to other potential surfaces, which can lead to chemical reactions other than the one of interest. DSC will be general because the nonresonant Stark effect is independent of the laser frequency and is applicable to all quantum systems.

The control of chemical reactions by lasers is an area of great interest (*1*–*3*). Quantum control can be viewed as chemistry where light is used as a photonic reagent (*4*). By contrast, we experimentally demonstrated that the nonresonant dynamic Stark effect participates in quantum control by altering reaction barriers, as if it were a photonic catalyst. Because all strong-field approaches tacitly contain the dynamic Stark effect, DSC can be considered as a fundamental element of the quantum control toolbox (*5*). However, by exclusively utilizing the dynamic Stark effect, DSC avoids the ionizing fields that can produce numerous competing processes, such as Coulomb explosion (*6*), enhanced ionization (*7*), and nonadiabatic multielectron ionization (*8*). Perturbative coherent control approaches do not modify potential energy surfaces but rather use interference between two or more real electric dipole transitions (*1*). Strong dipole coupling of states in nonper-

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turbative laser fields creates light-induced potentials that lead to phenomena such as static and transient bond hardening or softening (*3*, *9*). Optical pulses shaped by feedback-learning algorithms (*10*) can optimize, via multiphoton transitions, the yield of a chosen product, as demonstrated in the strong-field ionization-fragmentation of polyatomic molecules (*11*, *12*). Theoretical studies of laser catalysis (via electronic transitions) of ground-state collision processes investigated the line shape for the reaction probability as a function of optical frequency (*13*,*14*) or, alternatively, considered resonantly induced couplings during the collision (*15*). Moving wave packets between potential energy surfaces can likewise be used to avoid ground-state barriers (*2*).

To demonstrate DSC, we applied it to an important class of photochemical reactions: nonadiabatic processes. These processes, such as internal conversion or intersystem crossing, entail charge rearrangements that occur along a reaction path at the intersections of potential energy surfaces and act as triggers of the ensuing chemistry. Nonadiabatic processes are of paramount importance in the biological mechanisms of vision and photosynthesis and underlie the photochemistry of almost all polyatomic molecules (*16*). Chemical branching ratios in nonadiabatic processes are very sensitive to the intersection geometry, and therefore the dynamic modification of these processes is an important application of DSC. We specifically applied DSC to the canonical example of a nonadiabatic process, photodissociation of IBr (*17*–*19*). The reaction is initiated by absorption of a visible photon, making the transition from the ground state 1(X) to 2(B) (Fig. 1). The nonadiabatic intersection between states 2(B) and 3(Y) leads to two chemically distinct, neutral atomic channels: IBr → I + Br($^2P_{3/2}$) and I + Br*($^2P_{1/2}$). These Br and Br* atomic products have different chemical reactivity and play an important role in the destruction of ozone (*20*), especially in the marine boundary layer (*21*). An infrared DSC field was used to modify the curve-crossing barrier at a specific time, thus promoting the yield of one chosen product over another.

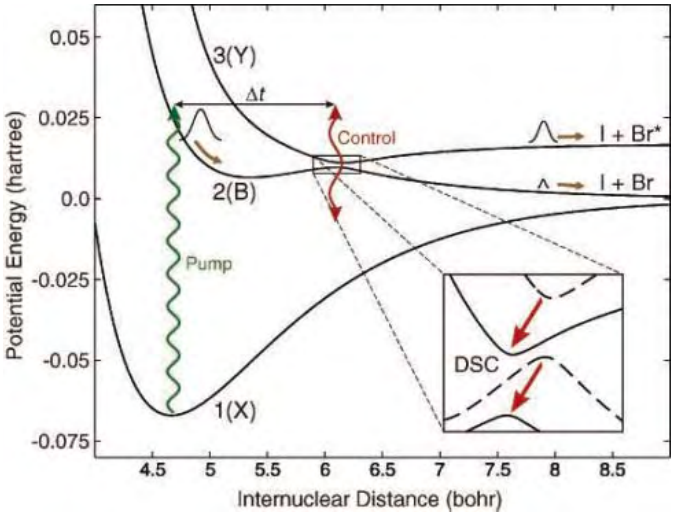

Fig. 1. DSC of IBr dissociation. An excited state wavepacket traversed a nonadiabatic crossing, correlating to either Br($^2P_{3/2}$) or Br*($^2P_{1/2}$) products. As the bond was breaking, an ultrafast IR field was used to dynamically modify the adiabatic potential barrier (**inset**) via the Stark effect, mediating the reaction outcome. Because no transitions to other electronic states were involved, the system always remained on these two coupled potentials.

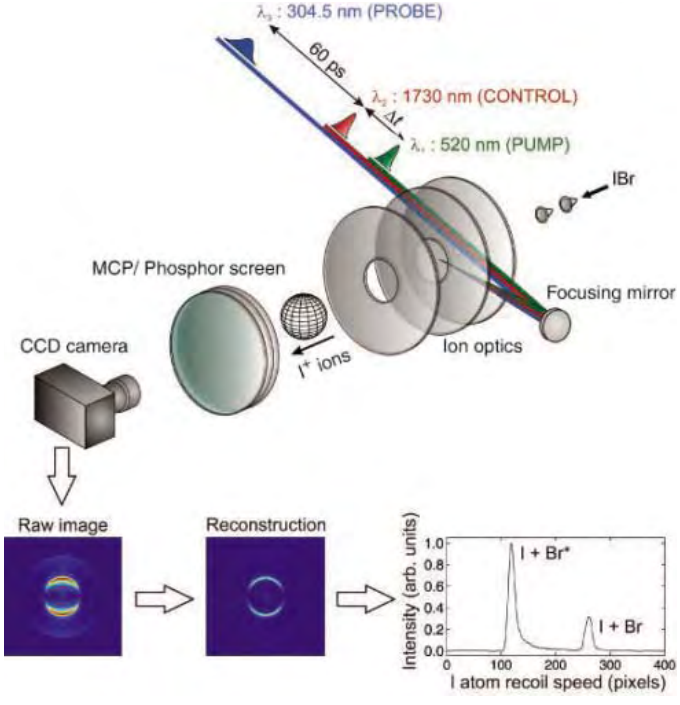

Fig. 2. Experimental demonstration of DSC of IBr dissociation. Dissociation of jet-cooled IBr was initiated with a 520-nm fs pulse. A delayed 1.7-μm fs control pulse was applied, modifying the reaction barrier and leading to a change in the chemical branching ratio. Long after dissociation, free neutral ground-state iodine atom products were ionized with a narrow band 304.5-nm laser. The recoiling ions were dispersed through the ion optics of a VMI spectrometer and imaged by a detector, and their velocity distributions were reconstructed. The iodine recoil velocity distribution directly reveals the Br*/Br branching ratio. The inner ring of the image corresponds to I+Br*, whereas the outer corresponds to I+Br production.

DSC of IBr photodissociation was demonstrated by using a molecular beam technique. Briefly described, a seeded supersonic jet of IBr in argon was produced by expansion through a 200-μm-diameter glass capillary nozzle (Fig. 2). Glass and polytetrafluoroethylene parts were used exclusively to avoid the decomposition of IBr. The reaction was initiated by a 100-fs laser pulse centered at 520 nm, above the dissociation limit for both channels. To achieve DSC, we focused a time-delayed 1.7-μm infrared pulse, 150 fs in duration, to nonperturbative intensities (*22*). To maximize the effects of DSC, we set the laser intensity to just below the threshold for ionization (i.e., below 10^{13} W/cm^2).

Importantly, a third weak laser field was used as the final probe of free neutral product formation. About 60 ps after the pump and catalysis pulses, free neutral ground-state iodine atoms produced in the reaction were selectively detected via (2+1) resonance-enhanced multiphoton ionization (REMPI) by using a 304.5-nm pulse of 0.4-nm linewidth. Conservation of energy and momentum dictate that the iodine fragments from the Br* channel have a lower velocity than those from the Br channel. Therefore, measurement of the iodine atom kinetic energy distribution permits unambiguous determination of the Br*/Br product branching ratio. This approach avoids uncertainties in the relative ionization cross sections of the chemically distinct Br and Br*. The velocity distribution of the iodine fragments was measured by using velocity map imaging (VMI), a charged-particle spectrometry technique that maps velocity to position, permitting the measurement of three-dimensional fragment velocity distributions (*23*).

A typical fourfold symmetrized velocity-mapped image was obtained under control-free conditions (i.e., 520-nm initiation and 304.5-nm I-atom probe beams only) and is presented along with its associated Abel inverted reconstruction and speed distribution (Fig. 2). The field-free branching ratio is Br*/Br = 3.5, in good agreement with previous measurements (*24*). Changes in the branching ratio due to the application of the infrared (IR) control field are easily and accurately determined from the VMI reconstructed speed distribution.

The mechanism underlying DSC's ability to reshape the potential energy barriers is the

nonresonant dynamic (or AC) Stark effect (*25*). This effect is similar to the well-known static (or DC) Stark effect but with several important distinctions. Infrared laser frequencies in the nonresonant 1.5- to 2-μm region are large with respect to rotational and vibrational frequencies but small with respect to electronic transition frequencies, and, hence, no single photon transitions can occur. In this situation, the dynamic Stark effect can be insensitive to the laser frequency, following instead the intensity envelope of the pulse (*26*). This property produces a quasi-static energy-level shift that reversibly follows the envelope of the laser pulse, avoiding all real electronic transitions (including ionization). The reaction Hamiltonian returns to its field-free form after the DSC pulse has passed, and, in this sense, DSC modifies the propagator during the propagation. Ultrafast lasers can produce vastly higher fields and more rapidly varying intensity envelopes than can DC electric field sources; therefore, they have the capacity to strongly shape a specific potential energy landscape on ultrafast time scales.

State intersection problems can be considered in two representations, the diabatic and the adiabatic, which are connected by a unitary transformation. In the limit of slow velocity along the reaction coordinate, the system follows the adiabatic potential. In the limit of high velocity, it follows the diabatic potential. The Landau-Zener (LZ) formalism offers insight into how DSC affects the curve-crossing probability (*27*). The simple LZ formula gives the probability for nonadiabatically hopping from one surface to another: $P = \exp\{-2\pi V_{23}^2/v\partial_R[V_2(R) - V_3(R)]\}$, where R is the reaction coordinate, v is the reaction coordinate velocity, V_{23} is the coupling between the channels, and the V_i terms are the diabatic potential energy surfaces. In IBr, the two diabatic curves correlate to atomic states that are not dipole coupled, and estimates suggest that the dipole coupling between these diabats is small compared with all other couplings (*28*). The parameters on which P depends are all influenced by the dynamic Stark effect. A key effect is the differential Stark shifting of the diabatic potential energy surfaces, which displaces the crossing point so that the coordinate velocity at the intersection is altered. DSC can also be understood in terms of the adiabatic potentials as $A_{2,3} = \frac{1}{2}(V_2 + V_3) \pm \frac{1}{2}\sqrt{(V_2 - V_3)^2 + 4V_{23}^2}$. The adiabatic potential barriers rise and fall as the diabats are Stark shifted, altering the wavepacket velocity and hence the hopping probability. Therefore, the simple LZ formula suggests that one can expect sensitive catalytic control by altering the barrier at the intersection.

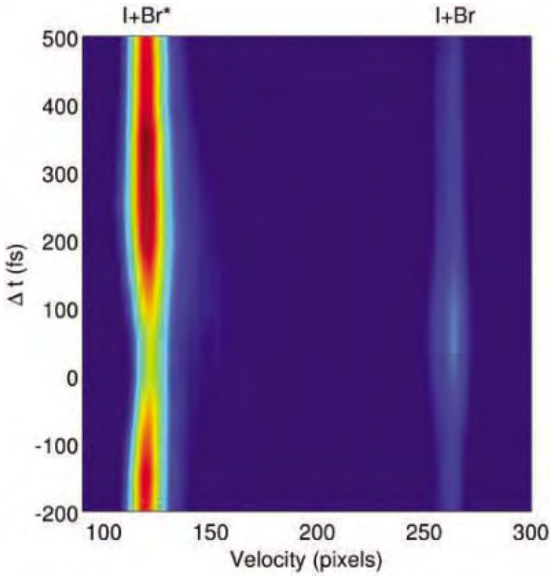

Fig. 3. Experimental iodine velocity distributions showing the two exit channels as a function of control pulse time delay. At each time delay Δt, the distribution is measured as in Fig. 2. By changing the control pulse delay, the branching fraction at the nonadiabatic crossing can be drastically altered. The smaller radius (velocity) corresponds to Br*; the higher, to Br. At early and late delays, the field-free branching ratio is observed, demonstrating the reversible nature of the DSC interaction.

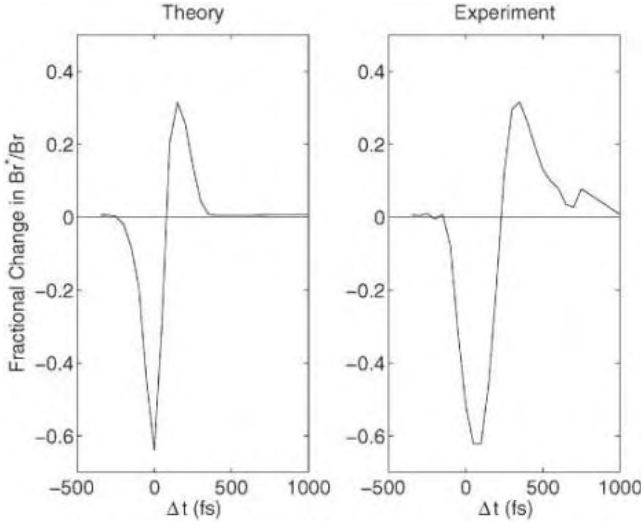

Fig. 4. Theoretical and experimental fractional changes in the branching ratio Br*/Br. The branching fraction is measured by taking the ratio of the integrated intensities of the two peaks in Fig. 3 as a function of Δt, the control-pulse time delay.

The raw I-atom speed distributions were plotted as a function of control pulse delay, Δt (Fig. 3). A key point is that at all delay times the recoil velocities of the I atom fragments remain essentially constant (i.e., follow vertical lines), demonstrating that IR control field has not excited new electronic states. There are two time delays when the reaction is critically sensitive to the control field: during initiation and during traversal of the crossing point. If the applied control pulse is simultaneous with the initiation pulse, the reaction begins on a Stark-shifted surface. The Stark lowering of the ground state has an effect equivalent to spectrally red-shifting the initiation wavelength. The result is that, as the control pulse fades, the wavepacket velocity is transiently reduced at the crossing point, decreasing the hopping probability and enhancing the Br channel. Application of the control pulse during traversal shifts and lowers the adiabatic barrier, thereby increasing the Landau-Zener hopping probability and thus production of Br*. Alternatively, in the diabatic picture, the crossing point shifts in the field, leading to a modified velocity at that point.

DSC is demonstrated by the variation of the overall integrated Br*/Br branching ratio as a function of IR pulse delay, Δt (Fig. 4). At early and late times, the speed distribution is identical to that of the molecule under field-free conditions. This result demonstrates the truly reversible nature of the DSC interaction: There are no real electronic or ionizing transitions due to the application of the control pulse. Application of the control field at Δt = 0 fs results in a 60% enhancement of Br yield at the expense of the Br* channel. Conversely, during control at Δt = 300 fs (traversal of the crossing), the reaction favors Br* production by more than 30%. The peak-to-valley contrast is over 90%, and, importantly, control is exerted on 100% of the reacting population. The experimental result is compared with numerical simulations based on a three-state split-operator approach, described elsewhere (*29*). The maximal Stark shifts used in the simulations are +0.125 eV for the diabatic $Y^3\Sigma^-(O^+)$ state and –0.022 eV for the diabatic $B^3\Pi(O^+)$ state. The simulation results are in good agreement

with experiment, and although the polarizabilities of the (relativistic) IBr states are difficult to calculate (*30*), DSC will always be possible if there are differential polarizabilities between states.

We have shown that the nonresonant dynamic Stark effect can be used to dynamically alter a potential energy barrier in a photochemical reaction, promoting the formation of a given product. Variants of DSC that incorporate Raman pumping will be applicable to ground-state reactions. Pulse-shaping methods from the quantum control toolbox will also prove useful. For example, implementing DSC with adaptive-feedback techniques will lead to the design of custom-shaped Stark-control laser pulses. As well, it will be possible to use interference effects in DSC to alter, for example, excited-state lifetimes (*29*). The frequency independence, the avoidance of excited state chemistry, and the universal applicability of the nonresonant dynamic Stark effect should prove important for scaling DSC to larger and more complex systems.

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22. The 1-kHz laser system consists of a Ti:Sapphire oscillator pumping a regenerative amplifier. The 800-nm output pumps a pair of optical parametric amplifiers (OPAs). The idler output from OPA1 (1730 nm) was used for the control pulse, whereas the signal (1485 nm) was mixed with residual 800-nm light to produce the 520-nm pump wavelength. The signal beam from OPA2 (1218 nm) was doubled and then doubled again to make the 304.5-nm ultraviolet (UV) probe. The REMPI probe is bandwidth-narrowed by use of long doubling crystals to ensure high selectivity. Telescopes were used to expand the three beams to varying diameters such that the focal-spot size ratios at the interaction region were UV:visible:IR = 1:1.5:2. Careful co-collimation then assured that the IR field was sampled at a uniform intensity.
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Coherent Dynamics of Coupled Electron and Nuclear Spin Qubits in Diamond

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Understanding and controlling the complex environment of solid-state quantum bits is a central challenge in spintronics and quantum information science. Coherent manipulation of an individual electron spin associated with a nitrogen-vacancy center in diamond was used to gain insight into its local environment. We show that this environment is effectively separated into a set of individual proximal ^{13}C nuclear spins, which are coupled coherently to the electron spin, and the remainder of the ^{13}C nuclear spins, which cause the loss of coherence. The proximal nuclear spins can be addressed and coupled individually because of quantum back-action from the electron, which modifies their energy levels and magnetic moments, effectively distinguishing them from the rest of the nuclei. These results open the door to coherent manipulation of individual isolated nuclear spins in a solid-state environment even at room temperature.

The controlled, coherent manipulation of quantum-mechanical systems is an important challenge in modern science and engineering (*1*). Solid-state quantum systems such as electronic spins (*2*–*10*), nuclear spins (*11*, *12*), and superconducting islands (*13*) are among the most promising candidates for realization of qubits. However, in contrast to isolated atomic systems (*14*), these solid-state qubits couple to a complex environment, which often leads to rapid loss of coherence and, in general, is difficult to understand (*15*–*19*).

We used spin-echo spectroscopy on a single-electron solid-state qubit to gain insight into its local environment. We investigated a single nitrogen-vacancy (NV) center in a high-purity diamond sample and showed that its electron spin coherence properties are determined by ^{13}C nuclear spins. Most importantly, we demonstrated that the electron spin couples coherently to individual proximal ^{13}C spins. By selecting an NV center with a desired nearby ^{13}C nucleus and adjusting the external magnetic field, we could effectively control the coupled electron-nuclear spin system. Our results show that it is possible to coherently address individual isolated nuclei in the solid state and manipulate them via a nearby electron spin. Because of the long coherence times of isolated nuclear spins (*20*), this is an important element of many solid-state quantum information approaches from quantum computing (*11*, *12*) to quantum repeaters (*21*, *22*).

Spin echo is widely used in bulk electron spin resonance (ESR) experiments to study interactions and to determine the structure of complex molecules (*23*). Recently, local contact interactions were observed between single-NV electronic spins and the nuclear spins associated with the host nitrogen and the nearest-neighbor carbon atoms (*3*, *24*). In the latter case, coherent dynamics of electron and nuclear spins were observed (*3*). We show that coherent coupling extends to separated isolated nuclei, which nominally constitute the electron environment and couple weakly to the electron spin.

The NV center stands out among solid-state systems because its electronic spin can be efficiently prepared, manipulated, and measured with optical and microwave excitation (*2*). The electronic ground state of the NV center is a spin triplet that exhibits a 2.87-GHz zero-field splitting, defining the $\hat{z}$ axis of the electron spin (Fig. 1A). Application of a small magnetic field splits the magnetic sublevels $m_s = \pm 1$, allowing selective microwave excitation of a single spin transition.

Our observations can be understood by considering how the NV electron spin interacts

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with a proximal spin-½ nucleus in the diamond lattice. If the electron spin is in the state with zero magnetic moment (m_s = 0), it does not interact with the nuclear spin, which is thereby free to precess under the influence of a small magnetic field applied externally. However, if the electron is in either of the m_s = ±1 states, then it generates a large local magnetic field that inhibits the free precession of nearby nuclei (*25*, *26*). Hence, the nuclear precession is conditional on the state of the electron. In particular, if the electron spin is prepared in a superposition state, then it becomes entangled with the nuclear spins at a rate determined by the external magnetic field, i.e., the Larmor frequency. In practice, the diamond lattice contains a large number of randomly placed nuclear spins. The electron becomes entangled with all of them and thus decoheres on the time scale of the Larmor period. Coherent coupling to individual proximal nuclear spins is nevertheless possible, because the electron spin effectively enhances their magnetic susceptibilities and hence their precession frequency.

In our experiments, single NV centers were isolated and addressed at room temperature by using optical scanning confocal microscopy (Fig. 1B) with excitation at 532 nm and fluorescence detection over the range from 650 to 800 nm. Each circled spot is a single NV center, which was verified by photon correlation measurements (inset). We investigated over 20 individual centers in detail, and where relevant we indicate which center we observed. The 532-nm excitation polarizes the spin triplet into the m_s = 0 state on the time scale of a few microseconds. After microwave manipulation of the spin, we detected the remaining population in the m_s = 0 state by again applying the excitation laser. Just after the 532-nm light is applied, the m_s = 0 state fluoresces more strongly than the m_s = ±1 states, allowing measurement of the spin (Fig. 1C) (*27*). Oscillations in fluorescence occur as a function of the duration of a microwave pulse resonant with the m_s = 0 to m_s = 1 transition (*2*) (Fig. 1D). These Rabi nutations should correspond to complete population transfer within the two-state system. Fluorescence data were thus normalized in units of m_s = 0 probability, p, where p = 1 and p = 0 correspond to the maximum and the minimum fluorescence, respectively, in a fit to Rabi oscillations observed under the same conditions.

To probe coherence properties of single electron spins, we make use of Ramsey spectroscopy and spin echo techniques (*28*). The free electron spin precession [Ramsey signal (*28*)] dephases on a fast time scale, T_2^* = 1.7 ± 0.2 μs (Fig. 1E). Moreover, the signal exhibits a complex oscillation pattern caused by level shifts from the host ^{14}N nucleus and other nearby spins (*27*). These frequency shifts can be eliminated by using a spin-echo (or Hahn echo) technique (*29*). It consists of the sequence $\pi/2 - \tau - \pi - \tau' - \pi/2$, where π represents a microwave pulse of sufficient duration to flip the electron spin from m_s = 0 to m_s = 1 and τ and τ' are durations of free precession intervals. When the two wait times are equal, $\tau = \tau'$, this sequence decouples the spin from an environment that changes slowly compared with τ (Fig. 2A). Decay of a typical Hahn echo signal (Fig. 2B) yielded a much longer coherence time, $\tau_C \approx 13 \pm 0.5\ \mu s \gg T_2^*/2$, thus indicating a long correlation (memory) time associated with the electron spin environment.

Spin-echo spectroscopy provides a useful tool for understanding this environment: By observing the spin-echo signal under varying conditions, we can indirectly determine the response of the environment and, from this, glean details about the environment itself. In particular, we observe that the echo signal depends on the magnetic field. As the magnetic field is increased, the initial decay of the spin echo signal occurs faster and faster. However, the signal revives at longer times, when τ equals τ_R (*30*). Figure 2C shows a typical spin-echo signal (center B) in moderate magnetic field as a function of time ($\tau = \tau'$). The initial collapse of the signal is followed by periodic revivals extending out to $2\tau \sim 240\ \mu s$. We find that the revival rate, $1/\tau_R$, precisely matches the Larmor precession frequency for ^{13}C nuclear spins of 1.071 kHz/G (Fig. 3A). This result indicates that the dominant environment of the NV electron spin is a nuclear spin bath formed by the spin-½ ^{13}C isotope, which exists in 1.1% abundance in the otherwise spinless ^{12}C diamond lattice (Fig. 3B). The ^{13}C precession induced periodic decorrelation and rephasing of the nuclear spin bath, which led to collapses and revivals of the electron spin-echo signal (Fig. 2C).

Every NV center studied exhibited spin-echo collapse and revival on long time scales, but many also showed more complicated evolution on short time scales. As an example, the spin-echo signal from NV center E (Fig. 4A) showed oscillations with slow and fast components at ~0.6 MHz and ~9 MHz, respectively. The fast component (referred to as the modulation frequency) was relatively insensitive to the magnetic field (Fig. 4B), but the slow component (envelope frequency) varied dramatically with the magnetic field amplitude and orientation (Fig. 4, C and D). These observations indicate that the electron spin gets periodically entangled and disentangled with an isolated system until the spin echo finally collapses from interactions with the precessing bulk spin bath. Although the data are not shown, some NV centers, for example NV C, exhibited several envelope and modulation

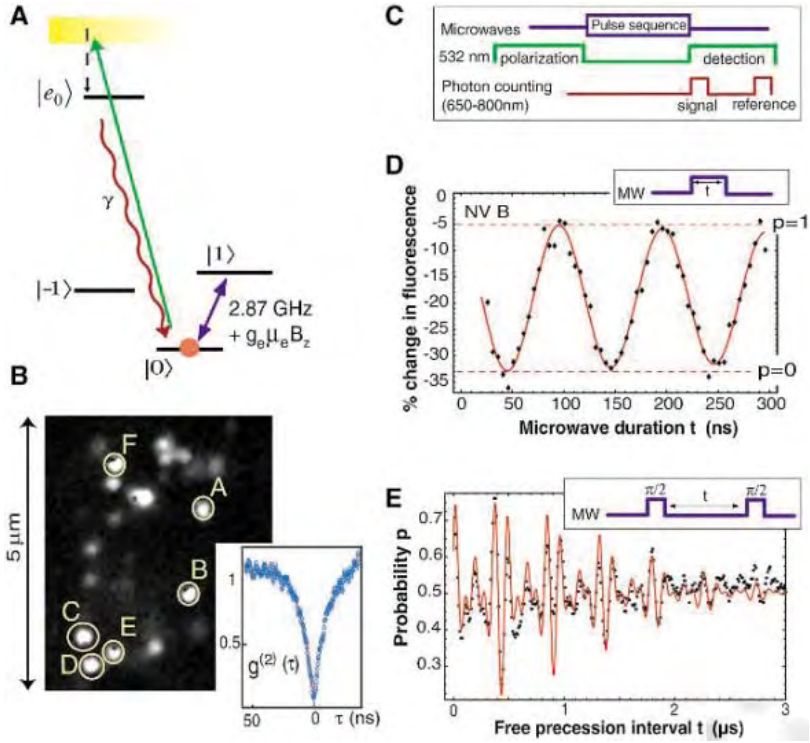

Fig. 1. (**A**) The energy level structure of the NV center. (**B**) Scanning confocal image showing locations of single NV centers A to F. (Inset) A representative measured auto-correlation function $g^{(2)}(\tau)$ from a single NV center, where $g^{(2)}(0) \ll ½$ indicates that we are exciting a single quantum emitter. (**C**) Experimental procedure. (**D**) Driven spin oscillations (Rabi nutations). The percent change in fluorescence between the signal and reference is observed as a function of resonant microwave (MW) pulse duration (inset) for NV center B. (**E**) Electron-spin free precession. The data were taken with a microwave detuning of 8 MHz as a function of delay between the two $\pi/2$ pulses (inset). The Ramsey signal was fitted (red) to $\exp[-(t/T_2^*)^2]\sum_{i=1}^{3}\cos(2\pi f_i t)$, where f_i values correspond to the level shifts from the host ^{14}N nuclear spin, obtaining $T_2^* = 1.7 \pm 0.2\ \mu s$.

frequencies, indicating that the electron spin interacts coherently with multiple ^{13}C nuclei. Other centers, for example NV F, showed no evidence of proximal ^{13}C spins.

To provide a quantitative explanation for these results, we first considered the spin-echo signal arising from a single ^{13}C nucleus $\mathbf{I}^{(j)}$ located a distance r_j in the direction $\mathbf{n}_j$ from the NV spin. This ^{13}C spin couples to the electron spin via the hyperfine interaction (*23*, *31*):

$$V^{(j)} = -\mu_e\mu_n \frac{8\pi|\psi_e(r_j)|^2}{3}\mathbf{S}\cdot\mathbf{I}^{(j)} + \left\langle \frac{\mu_e\mu_n}{r_j^3}\left\{\mathbf{S}\cdot\mathbf{I}^{(j)} - 3[\mathbf{n}_j\cdot\mathbf{S}][\mathbf{n}_j\cdot\mathbf{I}^{(j)}]\right\}\right\rangle \quad (1)$$

where μ_e and μ_n are the electron and nuclear magnetic moments, respectively, $|\psi_e(r_j)|^2$ is the electron spin density at the site of the nuclear spin, and angle brackets denote an average over the electron wavefunction, $\psi_e(r)$. The essence of this Hamiltonian, which can be represented as $V^{(j)} = \mathbf{B}^{(j)}_{ms}\cdot\mathbf{I}^{(j)}$, is that the nuclear spin experiences an effective magnetic field, $\mathbf{B}^{(j)}_{ms}$, that depends on the electron spin state m_s. This electron spin state–dependent magnetic field leads to conditional evolution of the nuclear spin, thereby entangling the two spins. Because of the spatial dependence of the hyperfine interaction, these effects decrease rapidly with distance from the NV center, making proximal nuclei stand out from the remainder of the spin bath.

The hyperfine interaction between the electron spin and a single nuclear spin has a dramatic effect on the spin-echo signal. After the initial $\pi/2$ pulse in the spin-echo sequence, the electron spin state $(|m_s = 0\rangle + |m_s = 1\rangle)/\sqrt{2}$ becomes entangled with the nuclear spin state at a rate determined by $\mathbf{B}^{(j)}_0$ and $\mathbf{B}^{(j)}_1$. As the electron spin becomes entangled with the nuclear spin, the spin-echo signal diminishes; when it gets disentangled, the signal revives. The resulting spin-echo signal thus exhibits periodic reductions in amplitude, with modulation frequencies $\omega_{j,ms}$ associated with each spin-dependent field $\mathbf{B}^{(j)}_{ms}$. By considering the unitary evolution associated with the dipole Hamiltonian [see, e.g., (*26*) for derivation], we obtained a simple expression for the spin echo signal, $p_j = (S_j + 1)/2$, with pseudospin S_j given by

$$S_j(\tau) = 1 - \frac{2|\mathbf{B}_0^{(j)} \times \mathbf{B}_1^{(j)}|^2}{|B_0^{(j)}|^2|B_1^{(j)}|^2} \times \sin^2(\omega_{j,0}\tau/2)\sin^2(\omega_{j,1}\tau/2) \quad (2)$$

Because the electron spin dipole field is stronger for $m_s = 1$, we associated $\omega_{j,1}$ with the fast modulation frequency and $\omega_{j,0}$ with the slower envelope frequency. Furthermore, we included multiple ^{13}C nuclei in our description by taking a sum over the dipole interactions, $V = \sum_j V^{(j)}$; the corresponding unitary evolution yields the echo signal $p = (S + 1)/2$ with $S = \prod_j S_j$.

We began with a simple treatment, which neglected the terms proportional to S_x and S_y because they are suppressed by the large electron-spin splitting $\Delta \approx 2.87$ GHz [the so-called secular approximation (*23*)]. In this model (Fig. 3C), the $m_s = 1$ nuclear-spin states have a fixed hyperfine splitting, $\omega_{j,1} \sim \mu_e\mu_n[\langle 1/r_j^3\rangle + 8\pi|\Psi_e(r_j)|^2/3]$, whereas the degenerate $m_s = 0$ nuclear-spin states can precess in a small applied magnetic field at the bare ^{13}C Larmor frequency $\omega_{j,0} = \omega_0$. When we included many nuclear spins in the echo signal, the fast echo modulations $\omega_{j,1}$ interfered with each other, causing initial decay of the signal as $\exp-(\tau/\tau_C)^4$. However, when $\tau = \tau' = 2\pi/\omega_0$, S_j equaled 1

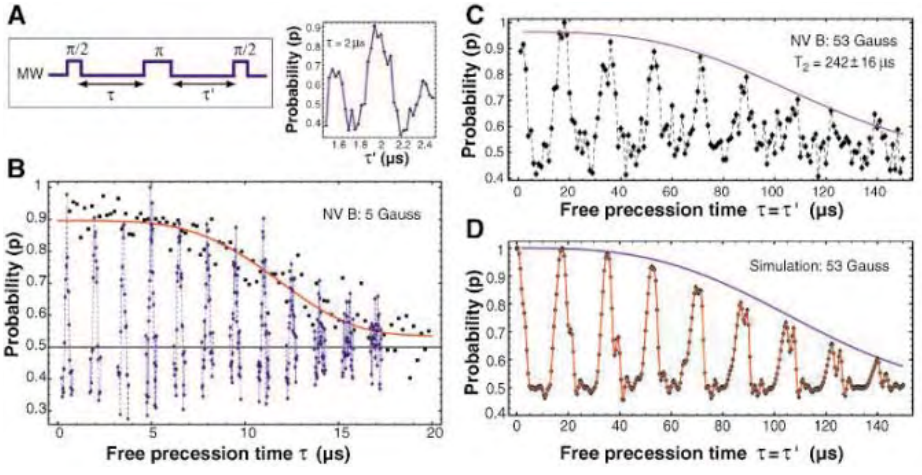

Fig. 2. (**A**) Spin echo. The spin-echo pulse sequence (left) is shown along with a representative time-resolved spin echo (right) from NV center B. A single spin echo is observed by holding τ fixed and varying τ'. (**B**) Spin echo decay for NV center B in a small magnetic field (B ~ 5 G). Individual echo peaks are mapped out by scanning τ' for several values of τ (blue curves). The envelope for the spin echoes (black squares), which we refer to as the spin-echo signal, maps out the peaks of the spin echoes. It is obtained by varying τ and τ' simultaneously so that $\tau = \tau'$ for each data point. The spin-echo signal is fitted to $\exp[-(\tau/\tau_c)^4]$ (red curve) to obtain the estimated coherence time $\tau_c = 13 \pm 0.5$ μs. (**C**) Collapse and revival of the spin-echo signal from NV center B in a moderate magnetic field (53 G). The decay of the revivals (blue curve) is found by fitting the height of each revival to $\exp[-(2\tau/T_2)^3]$, as would be expected from ^{13}C dipole-dipole induced dephasing (*24*, *31*), with $T_2 \approx 242 \pm 16$ μs. (**D**) Simulation of collapse and revival for an NV center in 53 G applied magnetic field, surrounded by a random distribution of 1.1% ^{13}C spins (*27*). Additional structure in the simulation arises from coherent interactions with the nearest ^{13}C in the lattice, via the same mechanism shown in Fig. 4. The phenomenological decay is added to the simulation for comparison with experimental data.

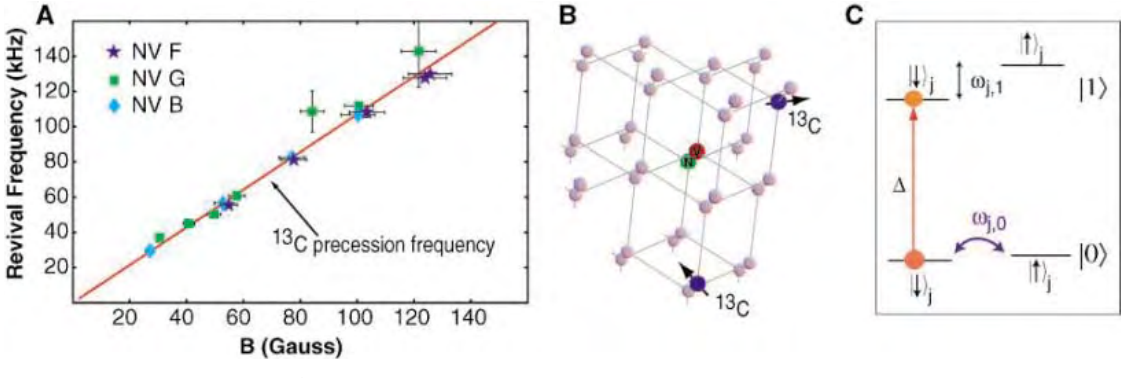

Fig. 3. (**A**) Spin-echo revival frequency as a function of magnetic field amplitude. Data from three representative centers—NV B, NV F, and NV G (not shown in Fig. 1B)—exhibit revivals that occur with the ^{13}C Larmor precession frequency (red). The data points for NV centers B and F were taken with $B \| \hat{z}$, whereas the data for NV center G were taken in a variety of magnetic field orientations. (**B**) Illustration of the ^{13}C environment surrounding the NV center. (**C**) Physical model for spin-echo modulation.

for all j, and the spin-echo signal revived. Simulations based on Eqs. 1 and 2 (Fig. 2D) are in good agreement with the observed collapses and revivals.

Such a simple picture cannot explain the observed echo modulation, however, because it predicts that the spin-echo signal should collapse before coherent interactions with individual ^{13}C spins become visible. In fact, the nonsecular terms in the Zeeman and dipole interactions slightly mix the electron-spin levels, introducing some electronic character to the nearby nuclear-spin levels and thus augmenting their magnetic moment by $\sim\mu_e(\omega_{j,1}/\Delta)$. Because $\mu_e \gg \mu_n$, this greatly enhances the nuclear Larmor precession rate for nearby spins. Furthermore, the enhancement is anisotropic: It is strongest when the external field is oriented perpendicular to the NV axis, corresponding to the largest degree of mixing. For a properly oriented magnetic field, proximal nuclei can thereby entangle and disentangle with the NV spin on time scales much faster than the bare ^{13}C Larmor period.

These theoretical predictions are in good agreement with our observations (Fig. 4). In addition, by fitting the envelope frequency as a function of magnetic field, we were able to estimate the six coupling parameters that characterize the hyperfine interaction (*27*). In principle, these parameters should also allow for precise determination of absolute nuclear position in the diamond lattice. However, direct comparison to the microscopic model depends sensitively on the details of the electronic wave function because of both the isotropic contact contribution and the averaged dipolar term in Eq. 1. Our results indicate that both terms can be important. For example, although the point dipole approximation yields results that are qualitatively similar to experimental data, it underestimates the coherent coupling strength as well as the echo collapse rate. At the same time, fits for NV centers D and E (Fig. 4, B to D, solid lines) indicate that some amount of anisotropic dipolar contribution is present (*27*). In fact, these fits yield an estimate of the electron-spin density at the positions of the proximal nuclei (*27*); by analyzing such data from a sufficiently large number of individual NV centers, it may be possible to determine the electronic wavefunction. This intriguing problem warrants future investigation.

Beyond providing a detailed insight into the mesoscopic environment of the spin qubit, our observations demonstrate a previously unknown mechanism for selective addressing and manipulation of single, isolated nuclear spins, even at room temperature. For example, such nuclear spins could be used as a resource for long-term storage of quantum information. They can be effectively manipulated via nearby electronic spins and potentially coupled together to explore a variety of proposed quantum information systems (*11*, *21*).

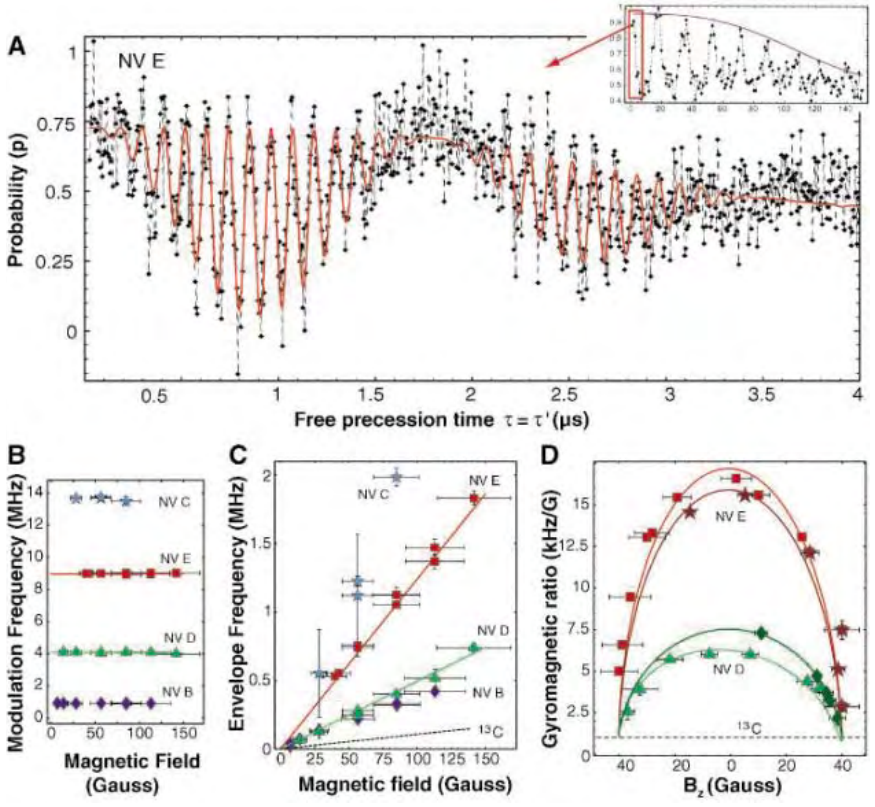

Fig. 4. (**A**) Spin-echo modulation as observed for NV E with B = 42 ± 6 G $\parallel -\hat{x} + \hat{z}$. The red curve represents a theoretical fit with the expected functional form $\exp[-(\tau/\tau_c)^4][a - b\sin(\omega_0\,\tau/2)^2\sin(\omega_1\,\tau/2)^2]$, yielding the modulation frequency $\omega_0 \sim 2\pi$ 9 MHz and envelope frequency $\omega_1 \sim 2\pi$ 0.6 MHz. (**B**) Modulation frequency for NV B to E as a function of magnetic field B $\parallel -\hat{x} + \hat{z}$. (**C**) Envelope frequency [same conditions as (B)]. The envelope frequencies are different for each center, but they all exceed the bare ^{13}C Larmor precession frequency (dashed line). (**D**) Effective gyromagnetic ratio (envelope frequency/magnetic field) versus magnetic field orientation for NV centers D and E. The amplitude of the magnetic field is fixed at 40 ± 4 G. The magnetic field is varied in the xz plane for NV center D (red boxes) and NV center E (green triangles) and yz plane for NV center D (dark red stars) and NV center E (dark green diamonds). Six free parameters that describe the interaction with the nearest ^{13}C spin were fit to the envelope and modulation frequency data (*27*), yielding the solid curves shown in (B) to (D). Error bars indicate a 95% confidence interval for fits to the data (y axis) and estimated error in magnetic field measurement (x axis) obtained from the discrepancy between Hall sensor measurements and the observed Zeeman splitting of the NV center.

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Rapid Early Development of Circumarctic Peatlands and Atmospheric CH_4 and CO_2 Variations

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An analysis of 1516 radiocarbon dates demonstrates that the development of the current circumarctic peatlands began ~16.5 thousand years ago (ka) and expanded explosively between 12 and 8 ka in concert with high summer insolation and increasing temperatures. Their rapid development contributed to the sustained peak in CH_4 and modest decline of CO_2 during the early Holocene and likely contributed to CH_4 and CO_2 fluctuations during earlier interglacial and interstadial transitions. Given the decreased tempo of peatland initiation in the late Holocene and the transition of many from fens (which generated high levels of CH_4) to ombrotrophic bogs, a neoglacial expansion of northern peatlands cannot explain the increase in atmospheric CH_4 that occurred after 6 ka.

Modern northern peatlands cover about 4 million km² across Eurasia and North America and represent the biggest wetland complex in the world (Fig. 1). Today, these peatlands are thought to store 180 to 455 Pg of sequestered carbon while also releasing 20 to 45 Tg per year of CH_4 into the atmosphere (*1*, *2*). The potential contribution of northern peatlands to fluctuations in atmospheric CH_4 and CO_2 over the late glacial and Holocene, and during earlier interglacials, has been a matter of much speculation and debate (*3*–*8*).

Ice-core records show that CH_4 concentrations rose from ~350 to 650 parts per billion by volume (ppbv) between the last glacial maximum (LGM), which occurred 20 ka (20,000 calendar years before C.E. 1950), and the Bølling-Allerød (BA) warm period (~15 to 13 ka). They then declined by ~200 ppbv during the Younger Dryas (YD) stadial (~13 to 11.5 ka), rose rapidly to levels over 700 ppbv in the early Holocene (11 to 8 ka), and then declined again between 8 and 6 ka (*3*). It has been maintained that because conditions were not favorable for widespread circumarctic peatland formation until after 8 ka, tropical wetlands or marine clathrates were the likely sources for the CH_4 peak that occurred 11 to 8 ka (*4*, *9*). On the basis of the assumed late-Holocene development, it has been suggested that northern peatlands played little role in the declining atmospheric CO_2, which has also been observed during the period from 11 to 8 ka (*5*). Others argue that the development of the northern peatland complex contributed substantially to the early-Holocene CH_4 increase and simultaneously decreased atmospheric CO_2 through carbon sequestration in northern soils (*6*–*8*).

Resolving the debate on the potential role of the northern peatlands in early postglacial CH_4 variations has become critical since the recent analysis of the deuterium and carbon isotopic composition of CH_4 (δD_{CH_4} and $\delta^{13}C_{CH_4}$) from Greenland ice samples, which suggested that the destabilization of marine clathrates is an unlikely explanation for the BA or early-Holocene CH_4 increases (*10*, *11*). In view of this evidence, it has been argued that the sustained high levels of CH_4 that developed at the close of the YD in part require a persistent terrestrial source linked to the warming climate at that time (*11*).

Holocene concentrations of atmospheric CH_4 reached a minimum of <600 ppbv at 6 ka and then increased again over the late Holocene to values of about 695 ppbv just before the industrial revolution (*3*). This late-Holocene increase has been variously attributed either to expansion of northern wetlands due to neoglacial climatic cooling after the Holocene thermal maximum (*4*) or to the product of expanding anthropogenic activity (particularly the expansion of rice- and cattle-based agrarian societies) in the mid- to late Holocene (*12*). However, recently collected CH_4 data from Antarctic ice cores reveal that the mid- to late-Holocene increase is not unique. A similar late-interglacial increase in Pleistocene atmospheric CH_4 occurred ~400 ka during Marine Isotope Stage 11 (MIS11), which clearly cannot reflect anthropogenic sources and has been ascribed instead to natural factors, including expansion of northern wetlands (*13*).

To address the hypothesis that northern peatland development could have contributed to the late-Pleistocene and Holocene variations in atmospheric CH_4 and CO_2 outlined above, we collated 1516 basal radiocarbon dates for peat initiation from wetlands throughout high-latitude Europe, Asia, and North America from a wide variety of sources (*14*). Some areas, such as Fennoscandia, have numerous basal dates for a small geographic area, whereas other very large areas such as central and eastern Siberia have a limited number of dates (Fig. 1). Therefore, we analyzed the compiled data set by raw number of initiation dates, and we also divided the Northern Hemisphere into grids of 2° latitude by 2° longitude and assigned a value for peatland initiation based on the oldest basal radiocarbon date in each cell (Fig. 1).

The lack of basal dates older than about 16.5 ka suggests that there was no extensive peatland complex in the northern circumpolar region during the LGM (Fig. 2). This finding is corroborated by palynological data that indicate a paucity of *Sphagnum* (peat moss) spores from deposits of this age (*15*). Before 16.5 ka, much of the North American and European arctic and subarctic were still covered in ice, and it is likely that the large ice-free areas of Siberia and Beringia were too cold and dry (*16*) to promote extensive peatland development. This absence of any significant northern peatland complex during the LGM is consistent with the depressed CH_4 levels and the relatively low proportion of northern CH_4 sources observed in ice-core records (Fig. 3).

In concert with increasing summer insolation and northern high-latitude temperatures, the current northern peatland complex began developing in ice-free portions of North America and Asia between 16.5 and 14 ka and initiating widely on all three northern continents after 14 ka (Figs. 1 and 2). These results dispel the earlier assertion that peatland development in

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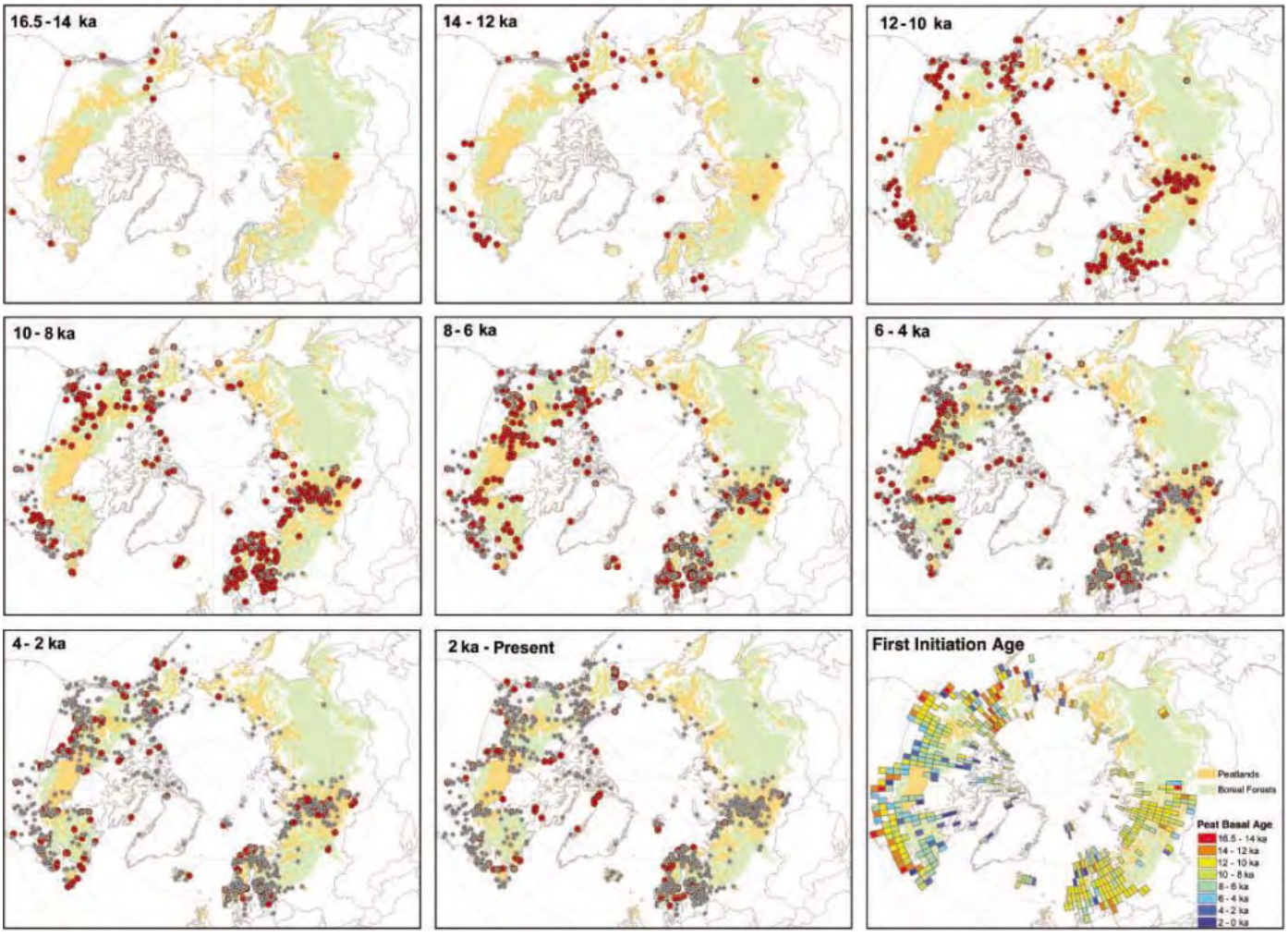

Fig. 1. Map of the current distribution of the northern circumarctic peatland complex and the boreal forest biome developed from a number of sources (SOM text) and the initiation dates of the peatlands based on radiocarbon dates from the base of peat deposits (*14*). The red dots indicate new peatlands that initiated during each time slice and the gray dots indicate preexisting peatlands initiated during earlier time slices. The timing of peatland initiation based on 2° by 2° grids is shown in the right panel in the bottom row. The grids map the oldest basal peat dates within each grid cell.

western Siberia was in advance of development in North America or elsewhere (*7*). The initial expansion coincides with warming during the BA period (Fig. 3), and it is likely that increasing warmth and moisture and decreasing glacial ice cover promoted peatland growth. Resultant development of the northern peatland complex corresponds with increasing atmospheric CH_4 concentrations observed during the BA (Fig. 3). However, the still-limited extent of northern peatlands at this early interval is consistent with evidence for a relatively restricted role of northern wetlands in producing the BA CH_4 increase (Fig. 3). There is a small decline in the rate of new peatland formation during the YD, which may be attributed to the development of cold conditions over much of the Northern Hemisphere and readvances of ice. At the same time, there is a precipitous drop in CH_4 recorded in the ice cores (Fig. 3) that seems to reflect additional factors. During the BA and YD periods, it is unlikely that the extent and growth of the northern peatlands was great enough to have significantly affected atmospheric CO_2 concentrations.

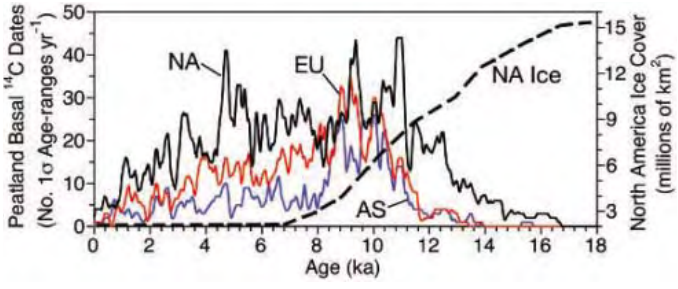

Fig. 2. Timing of circumarctic peatland establishment in North America (black), Europe (red), and Asia (blue) based on the total number of initiation dates from each region. The occurrence frequency of basal peat radiocarbon ages is plotted as the number of calibrated age ranges that fall in any year (*14*), smoothed with a 100-year running mean. The decreasing area of the Laurentide Ice Sheet (dashed line) as it retreated over the late glacial and Holocene (*17*) is also plotted.

The initiation of the early Holocene warming at 11.5 ka after the YD is marked by rapid expansion of peatlands throughout the north. The North American peatlands expanded rapidly during this time (Figs. 1 and 2), even though still constrained by the ice extent of the Laurentide Ice Sheet (*17*). The tempo of subsequent northern peatland development in North America was influenced by the rate of continued ice retreat and the exposure of land surfaces (Fig. 2). Large areas of northern Asia never supported ice during the LGM (*18*), and by 11 ka, high-latitude climate had warmed (Fig. 3). What remained of the Scandinavian Ice Sheet was restricted to cen-

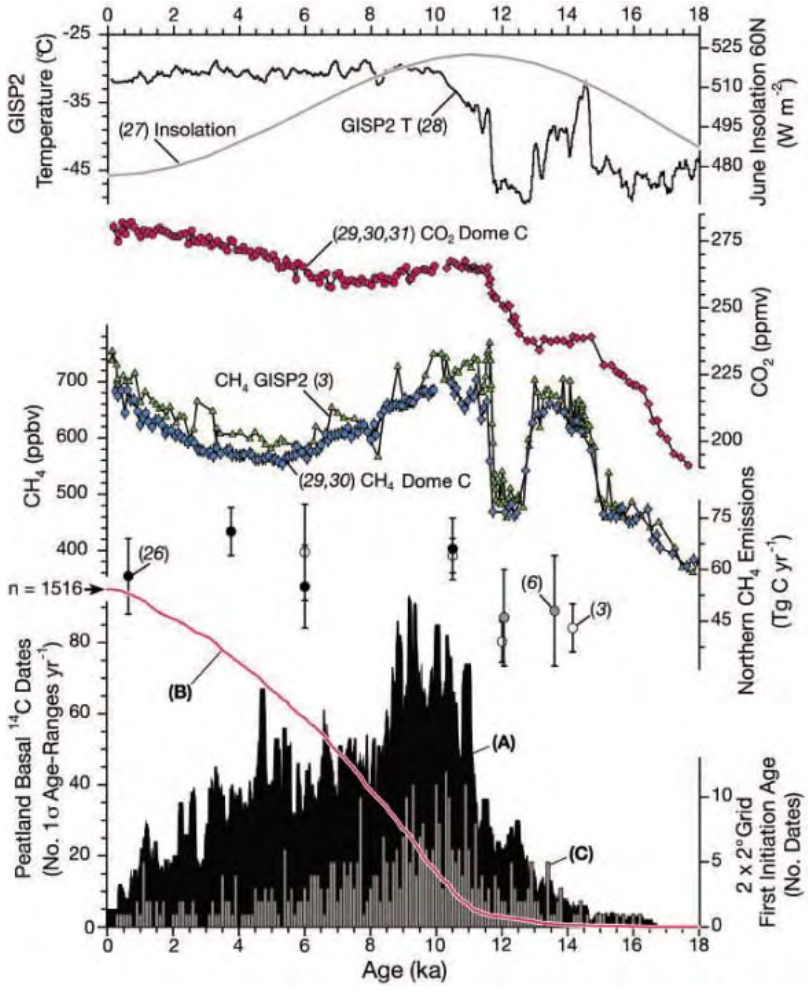

Fig. 3. Timing of circumarctic peatland establishment compared with June insolation at 60°N (*26*), Greenland Ice Sheet Project 2 (GISP2) temperature reconstruction (*27*), atmospheric CO_2 and CH_4 concentrations, and estimates of Northern Hemisphere CH_4 emissions derived from the InterPolar CH_4 Gradient (IPG) (*3*, *4*, *6*, *28*). Atmospheric CO_2 and CH_4 concentrations show ice-core data from European Project for Ice Coring in Antarctica (EPICA) Dome C (red for CO_2 and blue for CH_4) and GISP2 [green triangles show CH_4 (*3*, *29*–*31*)]. Dome C data are shown on the original EPICA Dome C 1 time scale from 0 to 10 ka before present (circles) and on the GISP2 time scale with CH_4 synchronization from 10 to 18 ka before present (diamonds; SOM text). Dome C error bars indicate 1σ uncertainty. (**A**) The occurrence frequency of 1516 radiocarbon dates of basal peat deposits (*14*) shows the number of calibrated age ranges that occur in any year (black curve). (**B**) Cumulative curve of 1516 dates (red curve). (**C**) The oldest basal peat dates within each 2° by 2° grid (gray bars).

tral Fennoscandia (*19*), allowing widespread expansion of peatlands in northern Eurasia (Figs. 1 and 2). A sustained period of maximum rates of peatland establishment followed and persisted until about 8 ka.

The rapid expansion of peatlands at the close of the YD coincides with a ~15-Tg increase in atmospheric CH_4 derived from the Northern Hemisphere (Fig. 3) and a 200- to 250-ppbv increase in total CH_4 concentrations. According to our data, the northern peatland complex was likely at <20% of its current aerial extent at the end of the YD and expanded to about 50% by 8 ka. On the basis of current estimates of overall CH_4 production from northern peatlands (*1*, *2*), they may have contributed 4 to 9 Tg of Northern Hemisphere CH_4 after the end of the YD and up to 12 to 27 Tg by 8 ka. However, based on typical peatland succession stages, higher summer insolation in the early Holocene, and evidence of peatland vegetation and type from our peat cores taken in Siberia (*7*), it is likely that many of these newly developed peatlands were warm and wet minerotrophic fens, often dominated by sedges. Such fens typically emit CH_4 at rates many times greater than the ombrotrophic *Sphagnum* bogs common in much of the north today (*6*, *20*–*22*). Therefore, we suspect that the rates of CH_4 production in northern peatlands may have been considerably higher in the early Holocene than they are today.

The $\delta^{13}C_{CH_4}$ values of ice from the Pakitsoq outcrop in western Greenland have been used to infer the likely origins of early-Holocene atmospheric CH_4 (*11*). It has been suggested that major terrestrial sources contributing methane during the period from 11 to 8 ka likely produced CH_4 with $\delta^{13}C$ values of between –50 and –60 (*11*). Although northern peatlands dominated by ombrogenous bogs may typically emit CH_4 with $\delta^{13}C < -60$, pore waters and emissions of boreal fens are relatively enriched in ^{13}C (average $\delta^{13}C_{CH_4}$ values of –50 to –60), particularly in high-productivity sites (*23*). These values are consistent with the early northern peatland complex, dominated by minerotrophic fens, which was a major contributor to the peak in CH_4 that occurred 11 to 8 ka and must be considered in addition to the potential tropical sources suggested previously (*11*).

The rapid growth of the circumarctic peatland complex and its associated sequestration of phytomass carbon in the early Holocene may have also contributed to the decline by ~7 parts per million by volume (ppmv) of atmospheric CO_2 observed in the ice-core records between 11 ka and the mid-Holocene (Fig. 3). This decline has been interpreted as reflecting a total biosphere uptake of 110 Pg C in the first half of the Holocene (*8*). More than half of the peatland basal dates in our data set are older than 8 ka, indicating rapid initiation and development of this carbon sink in the early Holocene. Conservatively, if by 8 ka peat deposits were 0.5 to 1 m thick, covered just one-quarter of today's peatland area, and were similar in carbon characteristics to today's northern peatlands (*1*), they would have been capable of sequestering 29 to 58 Pg C. Further detailed reconstruction of net peat accumulation rates during this period are required to better estimate the magnitude of the contribution of the northern peatlands to early-Holocene atmospheric CO_2 declines.

The widespread development of peatlands in response to increasing summer insolation, BA warming, and particularly rapid Holocene warming after the YD supports the hypothesis that the northern peatlands were a major terrestrial factor contributing to the early fluctuations in atmospheric CH_4 and to CO_2 sequestration during the current interglacial. It is likely that they played a similar role in earlier interglacials. The rapidity and large spatial extent of the response of the northern peatland complex, particularly to the onset of post-YD warming, suggests that they may even have played a role in CH_4 and CO_2 variations at the shorter time scale of earlier interstadials such as MIS3.

The observed decline in peatland initiation, particularly in Europe and Asia after 8 ka, corresponds to a decline in atmospheric CH_4 concentrations between 8 and 6 ka (Fig. 3). This decline in initiation rates should not be confused with a decline in total peatland area; most peatlands that were extant at 8 ka were still extant at 6 ka. However, many had trans-

formed from early minerotrophic fens to ombrotrophic *Sphagnum* bogs, which are typically weaker sources of CH_4 than are fens (*20*–*23*). Therefore, the transformation from high CH_4-efflux fens to *Sphagnum* bogs, coupled with a declining rate of new peatland formation, would have contributed to the decline in atmospheric CH_4. What remains puzzling is the role that northern peatlands played in the subsequent increase in CH_4 between 6 ka and just before the Industrial Revolution. By C.E. 1700, levels of atmospheric CH_4 had increased once again to almost 700 ppbv. However, contrary to earlier speculation (*9*, *15*), new peatland initiation was relatively modest in the late Holocene, and conversion of fens producing high levels of CH_4 to *Sphagnum* bogs with lower production was ongoing. If the mid- to late-Holocene CH_4 increase does not have an anthropogenic explanation, then its source must lie in factors other than large-scale resurgent expansion of the northern peatland complex.

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Supporting Online Material

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SOM Text
Table S1
References

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Gold in Magmatic Hydrothermal Solutions and the Rapid Formation of a Giant Ore Deposit

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The Ladolam hydrothermal system, on Lihir Island, Papua New Guinea, hosts one of the youngest and largest gold deposits in the world. Several deep (more than 1 kilometer) geothermal wells were drilled beneath the ore bodies to extract water at >275°C and to facilitate open-pit mining. Using a titanium down-hole sampler, we determined that the deep geothermal brine of magmatic origin contains ~15 parts per billion gold. At the current gold flux of 24 kilograms per year, this deposit could have formed within ~55,000 years. The combination of sustained metal flux and efficient metal precipitation led to the formation of a giant hydrothermal gold deposit in a short period.

The origins of giant hydrothermal gold deposits are enigmatic (*1*). This is because the concentrations of precious metals and flow rates of ore-forming fluids are poorly quantified, and the origins of the metals are unclear. These aspects can be clarified with direct analyses of fluids from modern hydrothermal systems. The only known active hydrothermal gold deposit is at Ladolam, on Lihir Island, Papua New Guinea, and this deposit is one of the largest in the world with ~1300 tons of gold. Geothermal drilling at Ladolam has been ongoing since before the start of open-pit mining in 1997, and the wells provide access to the deep fluids upstream of the ore zone. Because precious metals precipitate in the wells during fluid ascent due to boiling (*2*), we used a titanium down-hole sampler to obtain deep fluids for analyses (*3*). Any metals that precipitate in the sampler during its return to the surface can be incorporated into the water sample by rinsing the titanium sampler with strong acid. Thus, the deep metal concentrations can be directly measured and used to constrain the rate at which the gold is transported and then deposited in order to form this giant deposit. Because the isotopic compositions of the deep hydrothermal waters at Ladolam are predominantly magmatic in origin (*4*), our data cover not just the origin of the metals, but also the concentrations of gold and related metals in magmatic hydrothermal solutions, which are thought to be important to the formation of ore deposits (*5*, *6*).

The Ladolam gold deposit occupies the center of the extinct Luise volcano on Lihir Island (Fig. 1). The two major tabular ore zones cover ~2 km² and extend from the surface to 400 m below sea level. They lie in the middle of a breached crater that formed in response to sector collapse and unroofing of the volcanic edifice ~400,000 years ago (*4*, *7*, *8*). The resulting explosive depressurization of the magmatic-hydrothermal system produced a diatreme breccia complex and highly permeable rocks, which now host the ore. Mineralogical, fluid inclusion, and isotope studies (*4*) show that the gold was deposited in two stages between 150° and 250°C, from solutions of magmatic origin, when they mixed with other fluids or boiled. The magmatic gold-bearing solutions were near neutral to slightly alkaline pH and contained 5 to 10 wt % equivalent NaCl. The host rocks comprise alkalic mafic to intermediate volcanic and intrusive rocks (*9*) that have been hydro-

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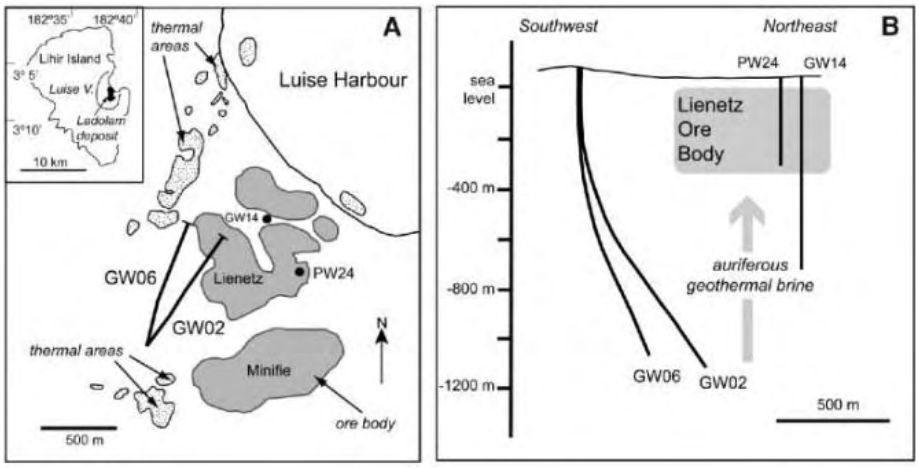

Fig. 1. (**A**) Location of the Ladolam gold deposit, ore bodies (Minifie and Lienetz), geothermal wells (GW06, GW02, GW14, and PW24), and thermal areas of surface discharge on Lihir Island. (**B**) Schematic southwest-northeast cross section showing the relation between geothermal wells sampled and the Lienetz ore body.

Table 1. Compositions of the deep geothermal brines from two wells.

Well	GW02	GW06
Enthalpy (J/g)	1100	1080
pH (lab)	7.36	8.01
	Aqueous species (ppm)	
Na	28,870	25,860
K	5,506	5,049
Ca	30	9.1
Mg		0.1
Fe	0.07	
Cl	21,710	21,300
SO_4	32,704	31,808
HCO_3	2,984	2,445
SiO_2	540	662
	Gases (mol/kg)	
CO_2	2.13×10^{-1}	1.46×10^{-1}
H_2S	6.04×10^{-4}	5.46×10^{-4}
CH_4	1.54×10^{-3}	1.05×10^{-3}
N_2	2.49×10^{-3}	1.63×10^{-3}
H_2	1.09×10^{-6}	3.25×10^{-5}

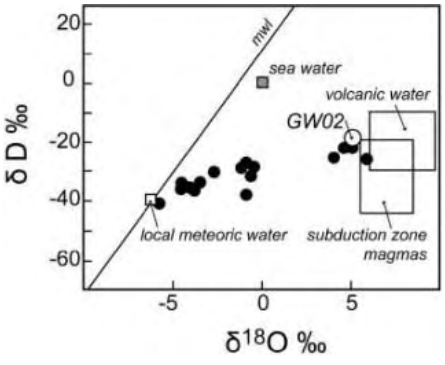

Fig. 2. Stable-isotope data for hydrothermal fluids from shallow wells (*4*); the composition of GW02 represents the deep geothermal brine containing water of predominantly magmatic origin. mwl, meteoric water line; the range of volcanic and subduction zone magmatic water is from (*5*).

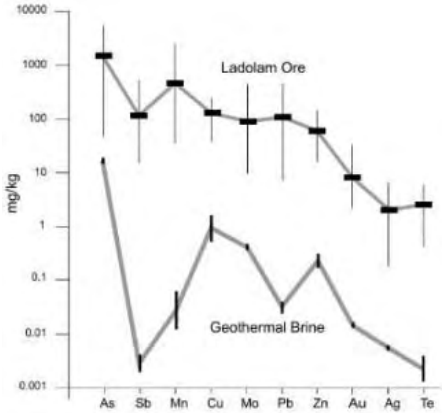

Fig. 3. Trace metal compositions (dark horizontal bar, average; vertical line, range) of Ladolam ores (*24*) compared to the compositions of deep geothermal brine.

thermally altered to quartz, potassium-feldspar, and pyrite, with or without illite, anhydrite, and calcite (*4*). This is an epithermal-style deposit affiliated with alkalic igneous rocks that formed in a young volcanic arc on the edge of back-arc basin (*4*, *10*–*12*).

The Ladolam hydrothermal system has an estimated heat flow of 50 to 70 MW, and hot water is ascending at ~50 kg/s (*13*), producing boiling springs and fumaroles on the northern and western edges of the main ore bodies and offshore in Luise Harbour (*4*, *14*). A number of shallow-to-deep geothermal wells were drilled to explore the hydrology of the system and to remove hot water from the mine site. The deepest wells terminate at >1 km below sea level in rocks with temperatures >275°C. On the basis of routine sampling and analysis of geothermal fluids, the deep liquid is oxidized and made up of predominantly magmatic water (Fig. 2), containing ~20,000 parts per million (ppm) Cl and ~30,000 ppm SO_4, and relatively low concentrations of H_2S (~6×10^{-4} mol/kg) and H_2 (~1×10^{-6} mol/kg) (Table 1). The deep well cuttings, containing potassium-feldspar, biotite, quartz, magnetite, pyrite, calcite, and anhydrite, indicate near-neutral pH of 6 to 7 at hydrothermal conditions. The modern deep geothermal sulfate-chloride brine thus resembles the ore-forming fluid.

We sampled four wells that penetrate beneath the northern edge of the Lienetz ore body (*15*): GW06 and GW02 are adjacent wells drilled to about 1100 m below sea level on parallel tracks that deviate to the northeast where maximum bottom-hole temperatures are >250°C; GW14 is a vertical well drilled to 700 m below sea level that had a maximum bottom-hole temperature of 260°C; PW24 is a shallow vertical well drilled to 350 m below sea level with a maximum down-hole temperature of 110°C. Assay values for deep drill cuttings (>400-m depth) from GW02 and GW06 range between 0.26 and 0.01 ppm Au, confirming that gold ore is restricted to shallow depths in the system.

The compositions of the solutions collected from GW06 and GW14 are similar and match the composition from GW02 (Table 2). The deep geothermal brine contains high gold concentrations [13 to 16 parts per billion (ppb) Au] (*3*), and these values greatly exceed those measured (0.05 to 0.2 ppb Au) in high-temperature submarine hydrothermal fluids (*16*). Except for Sb and Pb, the proportions of Au, Ag, Cu, Mo, Zn, and As in the deep geothermal brine match those in the ore (Fig. 3), suggesting that these elements were not fractionated during deposition. The concentrations of most trace metals, including gold, in the sulfate-chloride brine (2.4 wt % total dissolved salts) sampled at shallow depth from PW24 are much lower, and this solution has mixed with seawater and meteoric water as a consequence of well pumping.

At an ionic strength of 1.0, the Ladolam brine is at the limit of reliable hydrothermal speciation calculations, but pH, H_2S (aqueous), and H_2 (aqueous) are constrained by gas analyses (Table 1) and the mineral assemblage. Calculations based on these conditions and gold solubility data (*17*, *18*) suggest that the deep geothermal brine is between ~20 and 100% of gold saturation; however, the experiments on which the calculations were made are restricted to sulfate-poor, instead of sulfate-rich, solutions. If the deep brine is indeed undersaturated, then the gold budget, rather than the H_2S budget, of the system limits the gold concentration of the solution, as is the case for geothermal systems in New Zealand (*2*, *3*, *18*).

The Ladolam heat flow (50 to 70 MW) is modest compared with that of well-known geothermal systems such as Wairakei (420 MW) and Waiotapu (540 MW) in New Zealand (*19*).

Table 2. Major and trace metal analyses on down-hole brine samples from geothermal wells.

Well	GW02	GW06	GW06	PW24	PW24	GW14	GW14	Wairakei 212
Analysis	Major	Major	Trace metal	Major	Trace metal	Trace metal	Major	NZ field blank*
Date	29/09/2000	16/07/2002 a.m.	16/07/2002 p.m.	17/07/2002 p.m.	17/07/2002 p.m.	18/07/2002	26/05/2003	30/09/2002
Depth (m)	1,350	1,500	1,500	360	360	550	680	950
pH (lab)	7.12	8.58		6.76		8.69		
Cl (ppm)	19,860	19,700		7,000		19,336		
SO_4 (ppm)	31,255	31,380		7,511		29,605		
HCO_3 (ppm)	2,765	2,347		702		989		
Ag (ppb)			6		<1	5		0.6
As (ppm)	16.2	14.5	17	39	1.5	18	13.2	51
Au (ppb)			16		1	13		<0.1
B (ppm)	131	119	132	41	45	151	129	0.3
Br (ppm)			36		13	39		2,400
Cu (ppb)			4,450		10	1,590		22
Hg (ppb)			1			0.7		0.52
K (ppm)	4,842	4,490	4,200	1,491	1,440	4,900	5,057	<0.1
Mn (ppb)			620		4,900	120		38
Mo (ppb)			430		10	350		6
Na (ppm)	26,240	23,000	25,600	7,317	7,300	24,400	24,851	0.5
Pb (ppb)			23		<1	40		1.5
Sn (ppb)			840		11	590		7.7
Sb (ppb)			4		<1	2		19
Te (ppb)			<1		<1	4		0.4
Tl (ppb)			69		2	68		<0.1
V (ppb)			690		7	950		<0.01
Zn (ppb)			185		260	300		125

*New Zealand geothermal well: 610 ml of deionized water was added to the sampler and lowered to 950-m depth (255°C) for 10 min; the sampler was then returned to the surface to recover the blank, and aqua regia plus deionized water rinse were added, giving a total field blank sample of 770 ml.

The overall Ladolam gold flux is 24 kg/year, and only ~55,000 years would be required to account for all the known gold in the Ladolam ores if we assume constant aqueous gold concentration and fluid flow (50 kg/s), and 100% deposition. The Ladolam gold flux is similar to that at White Island (37 kg/year) (*20*) and less than that at Mt. Etna (80 to 1200 kg/year) (*21*), which are both active volcanoes, but greater than that at Broadlands-Ohaaki (5 kg/year) (*2*), which is a meteoric water-dominated geothermal system in New Zealand; these are the only other hydrothermal systems whose gold fluxes have been calculated, and they notably lack gold-ore deposits. Although the Ladolam gold concentrations are lower than a theoretical upper limit of 10,000 ppb, as determined by inclusion fluid analyses and calculations of magmatic hydrothermal solutions (*6*), the deep Ladolam brine is capable of forming a giant gold deposit within tens of thousands of years. For comparison, the giant epithermal deposit at Yanacocha, Peru (1320 tons of gold), comprises several widely spaced ore bodies, covering an area (~100 km^2) 50 times greater than Ladolam, emplaced in multiple episodes over 5 million years (*12*, *22*).

Our results indicate that a steady upward flux of gold, as a consequence of geothermal heat and mass transfer, followed by its efficient deposition at shallow depths, between <100 and 500 m, were critical in forming the Ladolam deposit in a compact volume of rock in a short period. The magmatic heritage of the oxidized geothermal brine, whose origin can be linked to deep dehydration of the subducted oceanic slab (*23*), was important for transporting gold into the near-surface ore-forming environment. That gold transport and deposition operated effectively and in concert on a time scale of several tens to possibly several hundreds of thousands of years emphasizes the importance of synchronizing these processes to generate a giant deposit.

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15. Fabricated completely of titanium, the down-hole sampler uses Viton o-rings and a nonreturn valve to seal the vessel once the hot fluid (>500 ml) is sampled. No evidence of leakage during recovery was observed. Before and after all the runs, the o-rings were replaced and the sampler was cleaned with aqua regia, using BDH Aristar acids, and deionized water (10^{18} ohms). After sampling, the water sample plus 80 ml of aqua regia and 80 ml of deionized water, which were used to rinse the sampler of any precipitates, were combined into a high-density polyethylene plastic bottle before analysis by inductively coupled plasma mass spectrometry at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) Energy Technology Centre for Advanced Analytical Chemistry in Lucas Heights, Australia. Sample PW24 was collected primarily to determine the major aqueous species, and only a 50-ml aliquot, with 1 ml of aqua regia added, was analyzed for trace metals. The restricted access to wells limited the number of down-hole samples obtained for trace-metal analyses and prevented replicate sampling or field blanks. GW06 was sampled on two consecutive days, first for major aqueous species and then for trace metals, followed by trace-metal sampling of PW24 and then GW14. Between 680 and 780 ml of clear liquid with trace sediment or precipitate was obtained in the sampling runs. The results and the order in which the wells were sampled indicate no cross-contamination and yield reproducible analyses of two distinct deepwater samples. A field blank from a New Zealand geothermal well, obtained with the same sampler under similar down-hole conditions, shows that background levels are well below the concentrations measured in the Ladolam geothermal brine (Table 2).
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Cellular and Subcellular Structure of Neoproterozoic Animal Embryos

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Stereoblastic embryos from the Doushantuo Formation of China exhibit occasional asynchronous cell division, with diminishing blastomere volume as cleavage proceeded. Asynchronous cell division is common in modern embryos, implying that sophisticated mechanisms for differential cell division timing and embryonic cell lineage differentiation evolved before 551 million years ago. Subcellular structures akin to organelles, coated yolk granules, or lipid vesicles occur in these embryos. Paired reniform structures within embryo cells may represent fossil evidence of cells about to undergo division. Embryos exhibit no evidence of epithelial organization, even in embryos composed of ~1000 cells. Many of these features are compatible with metazoans, but the absence of epithelialization is consistent only with a stem-metazoan affinity for Doushantuo embryos.

Fossilized embryos in the 635- to 551-million-year-old Doushantuo Formation of South China provide a record of embryology during the emergence of animal phyla (*1*, *2*). Based on interpreted cellular layers and polar lobe–like structures (*3*–*7*), a suite of putative blastulae, gastrulae, larvae, and minute adults has been described from the deposit. These fossils may also house cellular- and organelle-scale details of cleavage patterns of early animals (*8*).

Unfortunately, taphonomic and diagenetic artifacts are abundant in Doushantuo embryos. These include postmortem evidence for differential cell shrinkage, cytoplasmic decay, loss of cells and embryo envelopes, patchy organic matter degradation, multiple episodes of botryoidal void-filling cementation and dissolution, clotted fabric development, geopetal infilling, ambient pyrite trail formation, and mineral overgrowth (*9*–*12*). These features are rarely visible on the surface of embryos and are difficult to resolve in individual thin sections or in embryos lacking complete embryo envelopes. To constrain interpretations of metazoan affinity and resolve internal structures in these embryos, we identified a suite of 162 relatively pristine envelope-bound and spheroidal embryos in which recurrent biological structures and cleavage patterns could be distinguished from inorganic artifacts. We then used x-ray computed tomography (CT) in concert with scanning electron microscopy (SEM), transmission electron microscopy (TEM), and thin-section petrography to examine their internal morphology in three dimensions. Because variations in x-ray attenuation within embryos typically correspond to mineralogical or density variations associated with cell boundaries, subcellular structures, and diagenetic cements (*13*–*15*), it was possible to screen samples and identify recurrent biological features. The cellular and subcellular architecture of each embryo was volume-rendered to determine the number, arrangement, shape, and volume of cells in each embryo, and then compared with SEM, TEM, and thin-section petrography of similar samples [see supporting online material (SOM)].

Several interpretations of Doushantuo embryos have assumed that they follow the canonical pattern of progressive and synchronous cleavage (*1*, *16*, *17*). Using image stacks of x-ray attenuation through each embryo, we extracted three-dimensional (3D) isosurface models of each cell and counted the number of cells, including unexposed cells (Fig. 1). Embryos composed of more than 64 cells were difficult to count owing to diagenetic homogenization of some cell boundaries; these and embryos exhibiting shrinkage or breakage were excluded from our analysis. Although many specimens follow the expected 2^n pattern ($n = 42$ out of 57 specimens), as many as one in four deviate from this pattern ($n \geq 9$), being composed instead of 3, 5, 7, 9, 15, 24, and 31 cells (Fig. 2, fig. S1, and movie S1). Aberrant numbers of cells have been noted in previous studies of Doushantuo embryos, and the "extra cell" has been interpreted as a polar lobe (*6*, *7*). However, this explanation becomes less likely in later-stage embryos, in embryos that have fewer than the expected number of cells, and in embryos that deviate more substantially from the canonical pattern.

Deviation from the canonical 2^n pattern can result from taphonomical, pathological, or developmental processes. Taphonomic loss of cells and pathologic production of unequal-sized cells can result from degradation, anoxia, and toxicity, but such patterns are irregular and probably variable among individuals of the same species (*18*). Thus, pathologic and taphonomic causes may be excluded at least for Doushantuo embryos with regularly shaped cells, leaving developmental control as a possible explanation. Perhaps metazoan cleavage was less well organized and constrained in the Neoproterozoic, in comparison to living metazoans. Noncanonical cell numbers in marine embryos can result from several developmental processes (see SOM). Many are peculiar to unequally cleaving embryos, resulting from differences in cell division machinery that produce a large and a small daughter cell rather than two equal-sized ones. In addition, noncanonical cell numbers can result from asynchronous timing as a normal part of equally cleaving cell lineages. Asynchronous cleavage of cell lineages is widespread among metazoans. In such marine embryos, a 2^n cleavage pattern is followed, but because not all cell lineages divide at the same rate, the numbers of cells at any time do not necessarily match this count sequence.

We examined serial x-ray attenuation slices through the *x*, *y*, and *z* axes of a number of 2- to 32-cell embryos in order to identify cells that have distinct subcellular structures (*6*, *8*, *12*, *14*). The structures are typically characterized by a

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different degree of x-ray attenuation than the surrounding cellular material, suggesting that they differ in composition or density from the matrix (Fig. 3). There are two types of intracellular structures. The first are small spheres seen in various kinds of embryos, including two- and three-cell embryos that preserve distinct membranes (Fig. 3A and movie S2). The spheres differ from clotted and botryoidal fabrics and are coated by layers with relatively high x-ray absorption. Some spheres exhibit evidence of collapse and deflation (Fig. 3C). Internally, they are either empty or have a lower degree of x-ray attenuation than the surrounding matrix, and thin-sectioned samples indicate that their interiors are more organic-rich than the matrix. Together these features are consistent with apatitic encrustation of degrading organic spheres, which are comparable in shape and size to membrane-bound cytoplasmic vesicles, lipids, or yolk granules in the cleaving blastomeres of metazoans such as demosponges (*19*) and echinoids (Fig. 3B).

The second group (n = 10) consists of spheroidal-to-reniform structures, present as one or two per cell, as revealed by isosurface modeling (Fig. 3, D to G, and movies S3 and S4). In contrast to the first type, these show a slightly higher x-ray attenuation than the surrounding matrix. Mirror-image pairs of these structures have been observed in all cells of a four-cell embryo (Fig. 3E), but in only one cell of another (fig. S2), and single intracellular structures exist in some cells of 3-, 4-, 8- and 16-cell embryos (Figs. 1 and 2C, figs. S1 and S3, and movie S5). Thin-section petrography and TEM of epoxy-embedded four-cell specimens bearing these structures were performed (Fig. 3, F and G) and reveal that the reniform structures are more electron-dense, which is consistent with relative x-ray attenuation values. Together, these observations suggest early diagenetic replacement of a compositionally distinct zone in the center of the cell, rather than later-stage cavity infilling.

There are two possible interpretations for these paired structures. First, they may represent inorganically precipitated diagenetic or taphonomic features. Intracellular structures are well known in coccoidal cyanobacterial cells preserved in cherts of the Bitter Springs Formation of Australia, and these have been interpreted as degraded cytoplasmic bodies because of their highly variable size and morphology (*20*–*22*). Indeed, some of the much smaller Doushantuo algal cells also contain intracellular structures with variable morphologies (Fig. 3H), and some Doushantuo embryo cells contain eccentrically located internal bodies covered with botryoidal encrustation [for example, see figure 3.7 of (*16*)] that are best interpreted as degraded cytoplasm. However, the reniform subcellular structures of Doushantuo embryos have consistent size, occurrence, and location among the studied population and have diffuse margins that grade into surrounding matrix. They may represent fossilized nuclei, spindle bundles, or other organelles (*8*, *14*). The size, shape, and mirrored orientation of paired intracellular structures in four-cell embryos are similar to those of spindle bundles or divided nuclei formed during karyokinesis in extant metazoan embryos (*23*). The long axis of the reniform bodies is parallel to an anticipated cell division plane, which might pass through the junction of the two largest polyhedral cell faces.

Rotation of each embryo's polyhedral cell models (movie S4) reveals the packing topology of cells. Two-cell embryos typically have hemispherical cells. In four-cell embryos, each cell typically has one convex face (the exposed exterior surface) and three planar faces that correspond to its three neighboring cells (Fig. 3E and fig. S2). Three-, five-, seven-, and nine-cell embryos reveal evidence of the rearrangement of cell topology between adjacent 2^n stages (Fig. 2E), bearing out inferences of flexibility in cell membranes (*17*). In eight-cell embryos, each cell has four or five neighbors and planar interfaces (fig. S3). In 16-cell embryos, one of

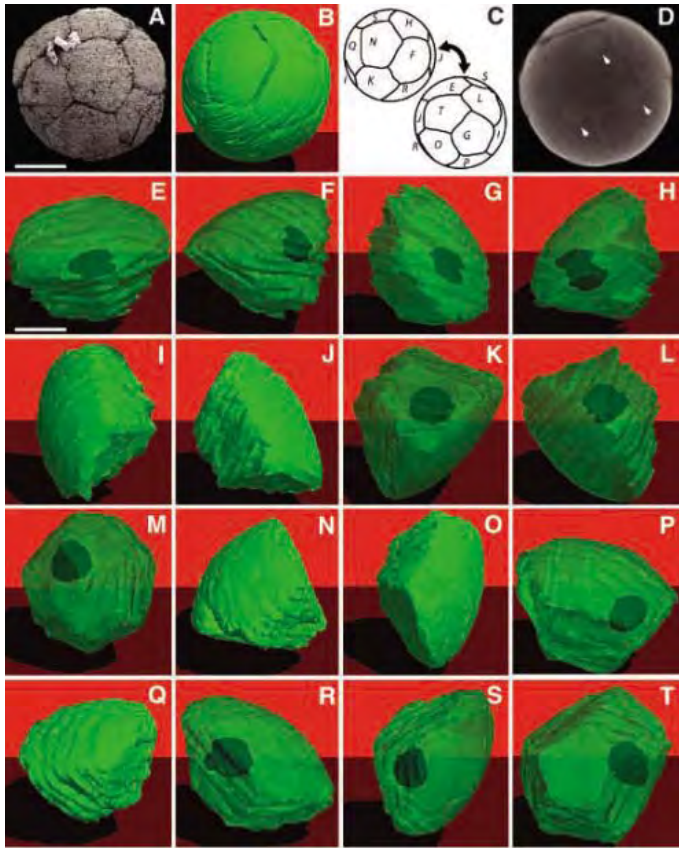

Fig. 1. (**A**) Scanning electron micrograph of a 16-cell embryo. (**B**) Isosurface model of the exterior of a 16-cell embryo (specimen DOU-10). (**C**) Schematic drawing with cells labeled to correspond to their models [(E) to (T)]. (**D**) An x-ray section showing very faint cell boundaries and subcellular spheroidal structures (arrowheads). Grayscale values in image have been inverted and the image placed on a black background to match (A). (**E** to **T**) Models of all 16 cells. Cells with intracellular structures (shaded dark green) are rendered transparent and those without are opaque. Corrugation on cell faces is an isocontouring artifact. (M) shows the internal cell. Scale bar in (A), 200 μm; in (E), 85 μm.

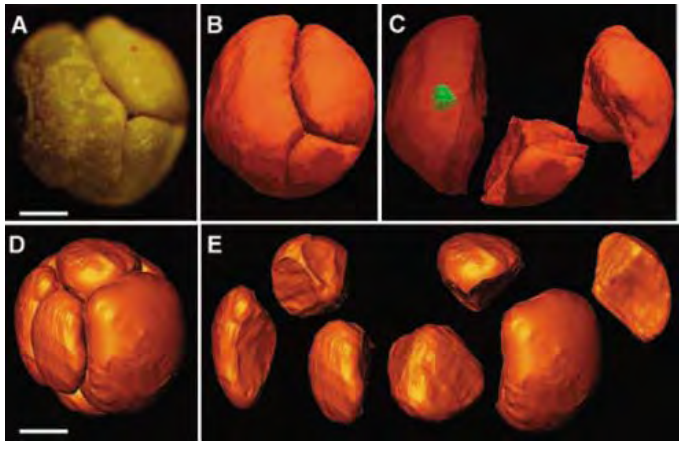

Fig. 2. Aberrant embryos. (**A**) Reflected-light photomicrograph of a 3-cell embryo (specimen DOU-25). (**B**) Exterior isosurface model. (**C**) Volume-rendered and extracted cell models, with the left cell rendered transparent to show the only subcellular structure (shaded green) in this embryo. (**D** and **E**) Seven-cell embryo (specimen MPLa). (D) Exterior isosurface model. (E) Volume renderings of each cell in (D). Cells in (C) and (E) are oriented in same position as they occur in (B) and (D). Scale bar in (A), 200 μm; in (D), 130 μm.

the cells sits in the center of the embryo and is surrounded by the remaining 15 cells, and thus has 15 planar faces (Fig. 1 and movie S5). The remaining exposed cells each have one convex exterior surface and six planar faces, which correspond to the five adjacent exposed cells and the internal cell. In embryos with ~32 cells, there are abundant many-faceted cells toward the exterior of the embryo, and many of these are more spheroidal than in earlier-stage embryos (movie S6). There are also several cells in the interior of each of these embryos, some of which are more elongate, pyramidal, or hourglass-shaped.

In many embryos composed of ~64 or more cells, the center is structureless, and embryos composed of hundreds to more than ~1000 cells still show no evidence of blastocoel formation or the organization of blastomeres into epithelia (fig. S4 and movie S7). Epithelialization, by whatever mechanism of gastrulation, should be underway in modern embryos with >100 cells.

The affinity of the embryos remains problematic because evidence of later developmental stages, juveniles, and adults is lacking, and because features in early developmental stages are often more widely distributed among animals than are those arising later in development (*24*). Despite hypotheses that Doushantuo embryos are unusual in comparison to most known metazoans (*25*), the patterns of cleavage and cell topology are compatible with a range of animal groups. For instance, in embryos composed of eight or more cells, the offset arrangement of successive tiers of cells, strong cell cohesion, and a stereoblastic cell topology are comparable to early cleavage embryos of many arthropod groups. Stereoblastulae are also particularly common among sponges (*26*) and scyphozoan cnidarians (*27*). Doushantuo embryos composed of many hundreds of cells resemble the purported gastrulae of demosponges, before the development of parenchymella larvae, although at this stage demosponges exhibit evidence of gastrulation, with a differentiated superficial layer of micromeres surrounding a core of macromeres (*19*).

None of the 162 embryos that we analyzed show any evidence of epithelial development. This absence of evidence is striking, given that the presence of subcellular structures in these fossils demonstrates a level of preservational fidelity comparable to that of the most celebrated fossil deposits (*28*). The absence of this 3D hallmark of sponge- and higher-grade metazoans (*29*, *30*) may indicate that they did not yet exist. Germ layers and tissue-grade structures suggested in Doushantuo microfossils (*3*–*5*) may instead be diagenetic artifacts (*9*–*11*). Together with topologic evidence and the absence of cell walls (*17*), which falsify an algal affinity, the combined observations suggest that the Doushantuo embryos are probably stem-group metazoans.

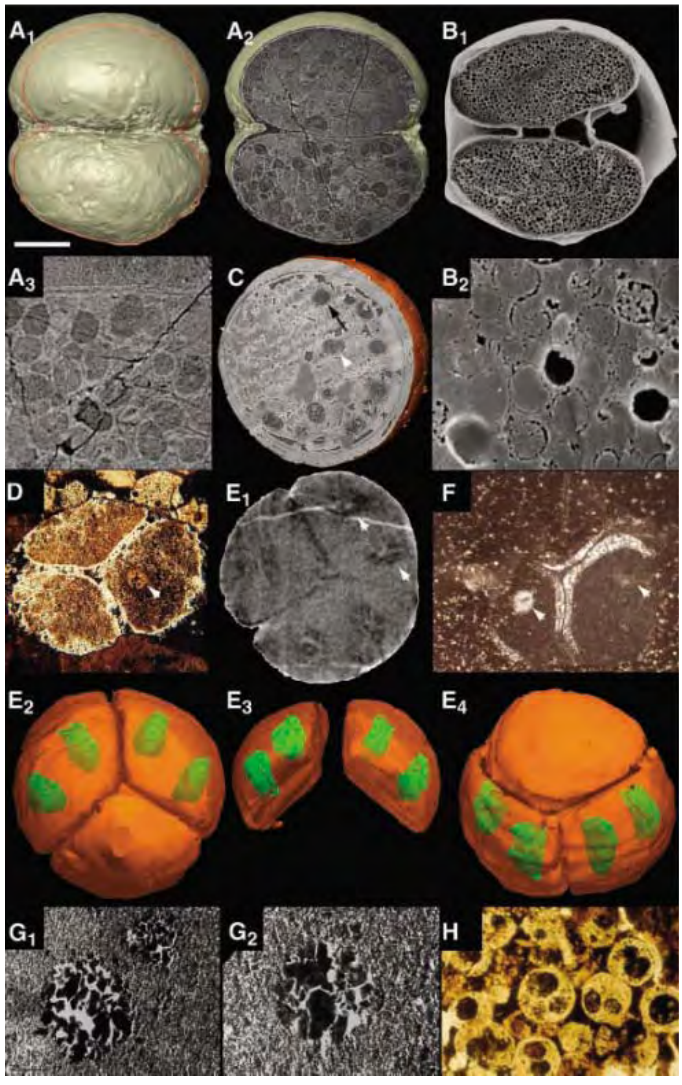

Fig. 3. (**A**) A two-cell embryo (specimen MPKxiv). (**A$_1$**) Surface rendering of the embryo based on tomographic scans, showing the position of the orthoslice (**A$_2$**), which reveals internal preservation of spheroidal subcellular structures analagous to modern lipid vesicles or yolk granules. (**A$_3$**) High magnification of an orthoslice at the boundary between the two cells. (**B$_1$** and **B$_2$**) Two-cell embryo of the sea urchin *Heliocidaris erythrogamma*, including an enlarged view of the lipid vesicles. Such vesicles are spheroidal and can be even larger in large-egged embryos of other modern invertebrates. (**C**) Orthosliced volume rendering of a possible embryo (specimen SB0604Clea), illustrating intact, deflated, and collapsed spheroidal and ovoidal interior structures, coated by several generations of cement. The left hemisphere is dominated by a clotted fabric. Representative deflated (white arrowhead) and collapsed (black arrow) spheres are indicated. Slices in (A) and (C) are negatives: Darker grayscale values represent lower x-ray attenuation. (**D** and **F**) Photomicrographs of four-cell embryos with subcellular structures (arrowheads). (F) Extracted, embedded, and thin-sectioned specimen. (**E$_1$**) X-ray section through a four-cell embryo (specimen DOU-8), showing three of the cells with paired subcellular structures (one pair is indicated by arrowheads), each with slightly greater attenuation (dark regions in image). (**E$_2$** to **E$_4$**) Isosurface models of the four tetrahedrally arranged cells, with two of the cells extracted. All cells have paired subcellular structures, but only the upper two cells are rendered transparent to show intracellular structures (shaded green). (E$_4$) Embryo from (E$_2$), rotated horizontally 180°. (**G**) TEM images of reniform (**G$_1$**) to spheroidal (**G$_2$**) structures like those in (D) to (F). Although the exact orientation of the embryo in (G$_1$) is poorly constrained because of difficulties inherent in sample embedding and microtoming, it is hypothesized that this represents a tangential section through a reniform subcellular structure, so that each kidney-shaped structure is represented by two subcircular, more electron-dense areas (dark regions in image). (**H**) Transmitted-light photomicrograph of much smaller algal or cyanobacterial cells, each with one or more intracellular structures that occupy much of each cell. Relative scale bar size is as follows: for (A) and (B), 170 μm; for (C), 270 μm; for (D), 150 μm; for (E), 150 μm; for (F), 190 μm; for (G$_1$), 8 μm; for (G$_2$), 5 μm; for (H), 20 μm.

References and Notes

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CDK2-Dependent Phosphorylation of FOXO1 as an Apoptotic Response to DNA Damage

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The function of cyclin-dependent kinase 2 (CDK2) is often abolished after DNA damage. The inhibition of CDK2 plays a central role in DNA damage–induced cell cycle arrest and DNA repair. However, whether CDK2 also influences the survival of cells under genotoxic stress is unknown. Forkhead box O (FOXO) transcription factors are emerging as key regulators of cell survival. CDK2 specifically phosphorylated FOXO1 at serine-249 (Ser^{249}) in vitro and in vivo. Phosphorylation of Ser^{249} resulted in cytoplasmic localization and inhibition of FOXO1. This phosphorylation was abrogated upon DNA damage through the cell cycle checkpoint pathway that is dependent on the protein kinases Chk1 and Chk2. Moreover, silencing of FOXO1 by small interfering RNA diminished DNA damage–induced death in both p53-deficient and p53-proficient cells. This effect was reversed by restored expression of FOXO1 in a manner depending on phosphorylation of Ser^{249}. Functional interaction between CDK2 and FOXO1 provides a mechanism that regulates apoptotic cell death after DNA strand breakage.

In response to DNA damage, mammalian cells activate checkpoint pathways that induce cell cycle delay or arrest. Delayed progression of the cell cycle allows time for either the repair of DNA damage or the elimination of genetically unstable cells by apoptosis. CDK2 is a key regulator of DNA damage–activated G_1 phase and intra–S phase checkpoints (*1*). DNA damage leads to the activation of several protein kinases, such as ataxia telangiectasia mutated (ATM), ataxia telangiectasia and Rad3 related (ATR), Chk1, and Chk2 (*2*), which eventually causes the p53-dependent transcription of the CDK inhibitor $p21^{WAF1}$ (*3*) or ubiquitin-dependent degradation of the protein phosphatase Cdc25A (*4*, *5*), or both, thereby inhibiting CDK2 activity and DNA replication. However, it is not clear whether CDK2 plays a role in the regulation of DNA damage–induced cell death.

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Activation of FOXO transcription factors induces apoptosis by up-regulating a number of cell death genes, including those encoding the ligand for the death receptor known as Fas or CD95, the Bcl-2–interacting mediator (*Bim*) of cell death, and the tumor necrosis factor–related apoptosis-inducing ligand (*6*–*8*). Increased expression of these pro-apoptotic proteins is required for cell death to be induced by the DNA damaging agent camptothecin or its derivatives (*9*, *10*). Because CDK2 is a key mediator of most checkpoint functions, we hypothesized that the activities of FOXO proteins might be regulated by DNA damage signals through functional interactions with CDK2. We therefore sought to determine whether CDK2 could phosphorylate the FOXO1 protein. Endogenous CDK2 proteins were immunoprecipitated from NIH 3T3 cells, and in vitro kinase assays were conducted with glutathione *S*-transferase (GST)–FOXO1 fusion proteins (Fig. 1A) as substrates. Two fragments of FOXO1, FO1-2 and FO1-3, were phosphorylated by immunoprecipitated CDK2 but not by control immunoprecipitates (Fig. 1B). The amount of FOXO1 phosphorylation was comparable to that of the C-terminal segment of retinoblastoma protein (RB), a well-characterized CDK2 substrate (Fig. 1B). No phosphorylation of the control GST protein was detected. Reconstituted complexes of purified bacterially produced GST-CDK2 with either GST–cyclin E or GST–cyclin A phosphorylated the same fragments of the FOXO1 protein as did the endogenous CDK2 (Fig. 1C). These effects were abolished when the CDK inhibitor $p27^{KIP1}$ was included (fig. S1A). These results indicate that CDK2 directly phosphorylates the FOXO1 protein in vitro.

CDK2 and other CDKs often recognize and phosphorylate the motif of serine or threonine followed by proline . Only one such site (Ser^{249}-Pro^{250}) exists in FO1-2. We demonstrated by in vitro kinase assays that CDK2 phosphorylates the FOXO1 protein at Ser^{249} and Ser^{298}, with a preference at Ser^{249} (Fig. 1D and fig. S1, C to E). These findings suggest that CDK2 phosphorylates FOXO1 primarily at the Ser^{249} residue within the consensus CDK-phosphorylation motif (fig. S1B).

To test whether FOXO1 is phosphorylated at Ser^{249} in vivo, we generated a phosphorylation-specific antibody against a peptide containing the phosphorylated Ser^{249}. The antibody specifically recognized the wild-type FOXO1 but not the Ser^{249}→Ala^{249} (S249A) mutant (Fig. 2A). This activity was blocked by a peptide containing the phosphorylated Ser^{249} but not by the corresponding nonphosphorylated peptide (fig. S2A). The antibody-mediated reaction was sensitive to the treatment of proteins with protein phosphatase (fig. S2B). Silencing of endogenous CDK2 by a pool of small interfering RNAs (siRNAs) led to a decrease in Ser^{249} phosphorylation (Fig. 2B). Moreover, phosphorylation of Ser^{249} was increased in cells transfected with an active CDK2 mutant, CDK2-Thr^{14}→Ala^{14}-Tyr^{15}→Phe^{15} (CDK2-AF), that is unable to undergo inhibitory phosphorylation (*5*) (fig. S2C). Furthermore, phosphorylation of Ser^{249} was low during the G_1 phase and increased as cells progressed through the S phase (Fig. 2C). Thus, these data indicate that CDK2 phosphorylates FOXO1 at Ser^{249} in vivo. CDK2 also interacts with the FOXO1 protein in vitro and in vivo (fig. S3).

FOXO1 functions primarily as a transcription factor. Ectopic expression of CDK2 and

cyclin E decreased the transcriptional activity of FOXO1 (Fig. 3A). The transcriptional activity of FOXO1 was largely enhanced by cotransfection of the tumor suppressor PTEN or by the conversion of its three Akt phosphorylation sites to alanine (FOXO1-AAA) in LNCaP prostate cancer cells, where phosphatase and tensin homolog (PTEN) is mutated and Akt is highly active. However, this effect was abolished by the expression of wild-type CDK2 but not by catalytically inactive kinase-dead CDK2-KD (Fig. 3, A and B). Notably, the effect of CDK2 was abrogated by treatment of cells with roscovitine, an inhibitor of CDK2 (Fig. 3B). Mutations in FOXO1 (S249A and S298A) that make it impervious to CDK2-mediated phosphorylation enhanced the activity of FOXO1-AAA, and the inhibitory effect of

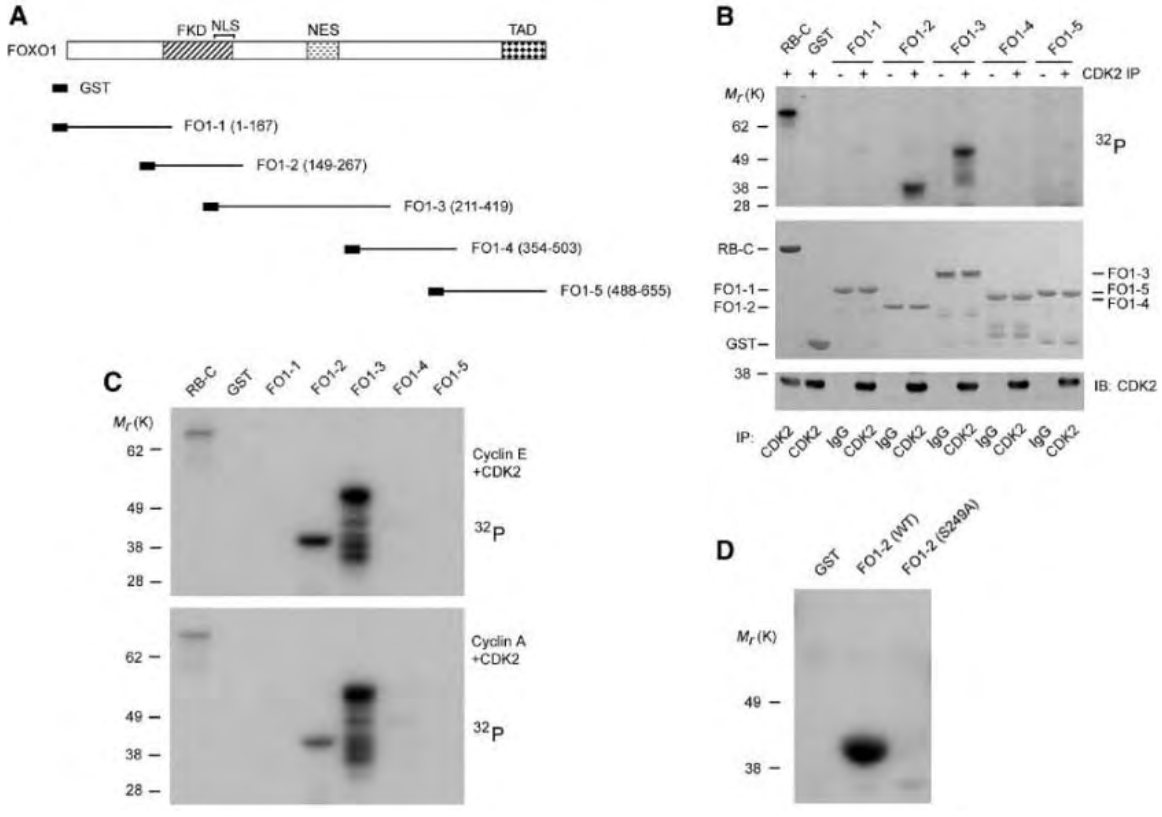

Fig. 1. CDK2 phosphorylates FOXO1 at Ser^{249} in vitro. (**A**) Schematic diagram of the five overlapping GST-FOXO1 fusion proteins, designated as FO1-1 to FO1-5. Numbers in parentheses show the start and end amino acid number of the FOXO1 fragment in each fusion protein. The forkhead DNA binding domain (FKD), nuclear localization signal domain (NLS), nuclear export signal domain (NES), and transactivation domain (TAD) of the protein are indicated. (**B**) (Top) In vitro kinase assays with immunoprecipitated (IP) CDK2. M_r(K), relative molecular weight (kilodaltons); ^{32}P, phosphorus-32. Immunoprecipitates of an antibody to CDK2 or nonspecific immunoglobulin G (IgG) from NIH 3T3 cells were used in kinase assays together with 2 μg of substrates: GST-FOXO1 fusion proteins, GST, or RB-C [a recombinant RB protein with its C-terminal segment (residues 701 to 928) fused to the maltose-binding protein]. (Middle) Protein substrates indicated by Coomassie blue staining. (Bottom) Immunoblotting (IB) of immunoprecipitated CDK2 in NIH 3T3 cells. (**C**) Reconstituted CDK2 kinase assays. Reconstituted cyclin E/CDK2 (0.12 μg, top) and reconstituted cyclin A/CDK2 (0.1 μg, bottom) were used in vitro in kinase assays with 0.2 μg of substrates. (**D**) Reconstituted cyclin E/CDK2 kinase assays with the use of the wild-type (WT) and S249A single–amino acid substitution mutant of FO1-2 as substrates.

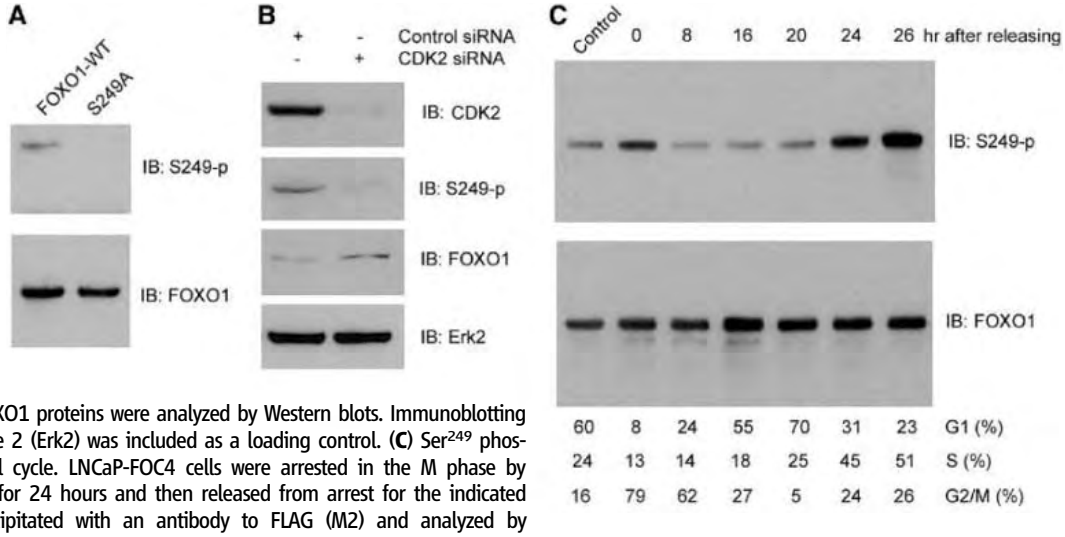

Fig. 2. CDK2 phosphorylates FOXO1 at Ser^{249} in vivo. (**A**) LNCaP cells were transfected with wild-type FLAG-tagged FOXO1 or S249A mutant. Ectopically expressed FOXO1 proteins were immunoprecipitated with an antibody to FLAG and blotted with an antibody against the phosphorylated FOXO1 at Ser^{249} (S249-p) or an antibody to FOXO1. (**B**) LNCaP cells were transfected with CDK2-specific siRNA or a nonspecific control siRNA. At 48 hours after transfection, the levels of endogenous CDK2, phosphorylated Ser^{249}, and total endogenous FOXO1 proteins were analyzed by Western blots. Immunoblotting of extracellular signal–regulated kinase 2 (Erk2) was included as a loading control. (**C**) Ser^{249} phosphorylation of FOXO1 during the cell cycle. LNCaP-FOC4 cells were arrested in the M phase by treatment with nocodazole (1 μg/ml) for 24 hours and then released from arrest for the indicated times. Cell lysates were immunoprecipitated with an antibody to FLAG (M2) and analyzed by immunoblotting as indicated. A cell cycle profile obtained from flow cytometry was also included.

CDK2 was abrogated in this double mutant (Fig. 3B). The transcription activity of FOXO1 was largely diminished by a phosphomimicking mutation at Ser^{249} (Ser^{249}→Asp^{249}) (fig. S4D). Taken together, these results suggest that CDK2-induced inhibition of transcriptional activity of FOXO1 is mediated primarily by the phosphorylation of Ser^{249}. Expression of endogenous FOXO-activated genes, including *p27^{KIP1}*, *Bim*, and manganese superoxide dismutase (*7*, *11*, *12*), was increased by inhibition of CDK2 (figs. S5C and S6, A and B). Moreover, Ser^{249} was adjacent to the three-arginine motif (fig. S6D), which is critical for nuclear localization of FOXO proteins (*13*). Overexpression of CDK2 resulted in the cytoplasmic localization of wild-type FOXO1 but not the phosphorylation-resistant mutant S249A of FOXO1 (Fig. 3, C and D), suggesting that CDK2-induced trafficking of FOXO1 from the nucleus to the cytoplasm may be mediated by phosphorylation at Ser^{249}.

Camptothecin is a DNA damaging agent that inhibits the religation function of topoisomerase I by inducing the covalent attachment of topoisomerase I to DNA. This effect results in the activation of the DNA double-strand break checkpoint pathways and inhibition of CDK2 activity. Camptothecin treatment inhibited the activity of CDK2 in DU145 prostate cancer cells (Fig. 4A). Phosphorylation of endogenous FOXO1 at Ser^{249} was also abolished (Fig. 4A). Camptothecin treatment also diminished the phosphorylation of FLAG-FOXO1 at Ser^{249} in both LNCaP and PC-3 prostate cancer cells (Fig. 4B and fig. S7, A and B). Phosphorylation of FOXO1 at Ser^{249} also decreased in LNCaP cells exposed to γ irradiation (fig. S7C). Because neither DU145 nor PC-3 cell lines express functional p53 (*14*), these data suggest that CDK2-mediated phosphorylation of FOXO1 can be inhibited by DNA damaging agents through a p53-independent mechanism.

Genotoxic agents inhibit the activity of CDK2 through a checkpoint signaling pathway that includes the protein kinases ATM and ATR, Chk1 and Chk2, and the protein phosphatase Cdc25A independently of the p53-p21^{WAF1}

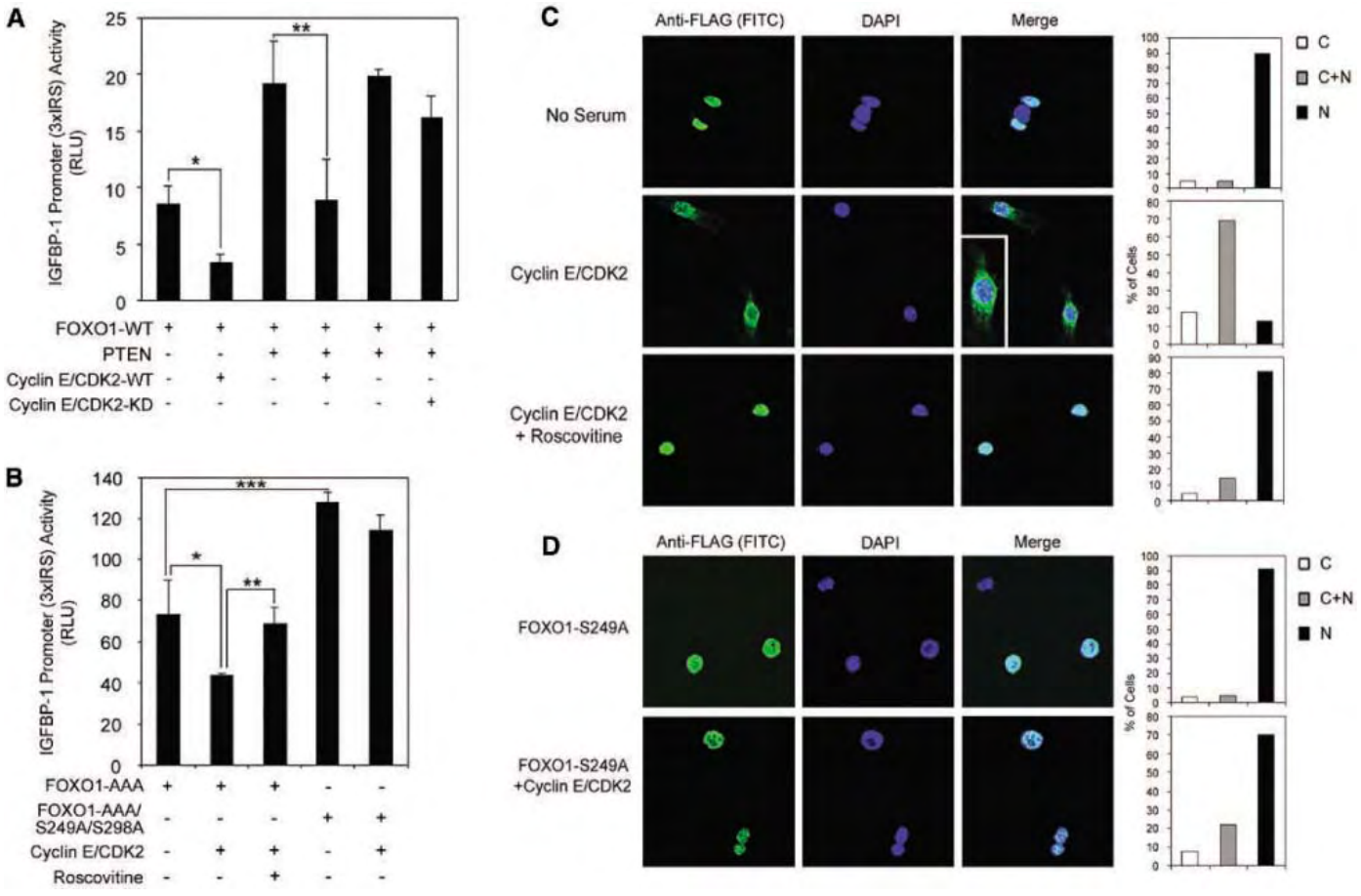

Fig. 3. CDK2 inhibits FOXO1 through Ser^{249} phosphorylation. (**A**) Effect of CDK2 on PTEN-induced activation of FOXO1. LNCaP cells were cotransfected with a FOXO1 luciferase reporter construct containing three copies of the insulin-responsive sequence (3xIRS), and the plasmids are indicated. Luciferase activities were measured at 36 hours after transfection. The relative luciferase units (RLU) were determined by normalizing the measured units of firefly luciferase with the measured renilla luciferase activity. *P = 0.024; **P = 0.027. (**B**) Effect of mutations at the CDK2 phosphorylation sites in FOXO1 on its transcriptional activity. LNCaP cells were transfected with plasmids as indicated. Cells were treated with the CDK2 inhibitor roscovitine (15 μM) or vehicle at 24 hours after transfection. Cell lysates were subjected to luciferase assays at 48 hours after transfection. Luciferase measurement was performed as in (A). *P = 0.017; **P = 0.005; ***P = 0.002. Error bars in (A) and (B) indicate SD among three individual experiments. (**C**) Cellular localization of ectopically expressed wild-type FOXO1 in DU145 cells, which is a PTEN-positive cell line, and cellular localization of FOXO proteins are minimally affected by Akt. Plasmids for FLAG-FOXO1 were cotransfected with cyclin E and CDK2, or with an empty vector into DU145 cells. At 36 hours after transfection, cells were serum-starved for 24 hours. Cells were treated with roscovitine (40 μM) or vehicle for 3 hours before cells were subjected to immunofluorescent chemistry. Quantification of a representative experiment is shown (bar graphs). C, cytoplasm; C+N, cytoplasm and nucleus; N, nucleus. Similar results were obtained from three independent experiments. Inset on merge picture in the middle panel shows the staining of a cell with fluorescein isothiocyanate (FITC)–conjugated antibody to FLAG in higher magnification. DAPI, 4′,6′-diamidino-2-phenylindole. (**D**) Effect of CDK2 on the cellular localization of ectopically expressed FOXO1-S249A mutant in DU145 cells. Cells were transfected with plasmids as indicated and analyzed as in (C).

pathway (*4*, *5*). To determine whether the Chk1 and Chk2 proteins function in regulating FOXO1 phosphorylation at Ser[249], we silenced endogenous Chk1 in LNCaP cells or treated them with the Chk1 inhibitor UCN-01. Not only did the basal amount of FOXO1 phosphorylation at Ser[249] increase, but the camptothecin-induced decrease in FOXO1 phosphorylation was also partially blocked (Fig. 4B and fig. S7D). Moreover, silencing of Chk2 by two independent siRNAs diminished the camptothecin-induced decrease in Ser[249] phosphorylation of FOXO1 (fig. S7E). These findings indicate that DNA damaging agents regulate FOXO1, at least in part, by controlling the Chk1- or Chk2-dependent signaling pathways.

Silencing of FOXO1, but not of FOXO3a or FOXO4, markedly diminished camptothecin-induced cell death (Fig. 4C and figs. S9F and S10A). Camptothecin-induced apoptosis was restored by forced expression of silencing-resistant FOXO1 proteins (FOXO1-WT[sr] or FOXO1-S249A[sr]). The effect of FOXO1-WT[sr], but not FOXO1-S249A[sr], was inhibited by the CDK2-AF mutant (Fig. 4C). Forced expression of FOXO3a or FOXO4 also restored DNA damage–induced apoptosis in cells with silencing of FOXO1, and this effect was not blocked by the expression of CDK2-AF (Fig. 4C and fig. S10B). This observation was not unexpected, given that FOXO factors share the same binding sequences of target genes (*15*) and that the functions of FOXO3a and FOXO4 were not regulated by CDK2 (fig. S9, A to F). In addition, the effect of FOXO1 on DNA damage–induced apoptosis was consistent with its transcriptional activities (fig. S10C). FOXO1-mediated cell death was also observed in p53-proficient cells, including the MCF7 breast cancer line, the "normal" (nontumorigenic) MCF10A breast epithelial cell line, and wild-type mouse embryonic fibroblasts (fig. S11, A to D). Thus, FOXO1 contributes to DNA damage–induced apoptosis in both p53-deficient and p53-proficient cells, especially in tumor cells. Activation of FOXO proteins (for example, FOXO4) but not p53 also mediates tumor-specific cell death that results from the silencing of sirtuin homolog 1, a regulator of p53 and FOXO pathways in response to stress (*16*). Thus, it is important to dissect the roles of individual FOXO proteins in the selective killing of tumor cells under genotoxic and metabolic stress conditions.

The DNA damage response functions as a biological barrier that inhibits cancer progression (*17*, *18*). Defects in this pathway often allow human cancers to progress through the CDK2-dependent pathways (*5*). Cyclin E, another regulator of CDK2, is often deregulated in cancer (*19*). Deregulation of cyclin E and defects in the DNA damage signaling networks may synergistically favor the survival of nascent cancer cells and therefore promote tumorigenesis through the inhibition of FOXO1. Given that the FOXO1 mechanism can be restored by cancer therapeutic agents, such as γ irradiation and chemotherapeutic drugs, CDK2-mediated regulation of FOXO1 represents a previously unrecognized pathway (Fig. 4D) that links DNA damage to cell death (*4*, *5*, *20*).

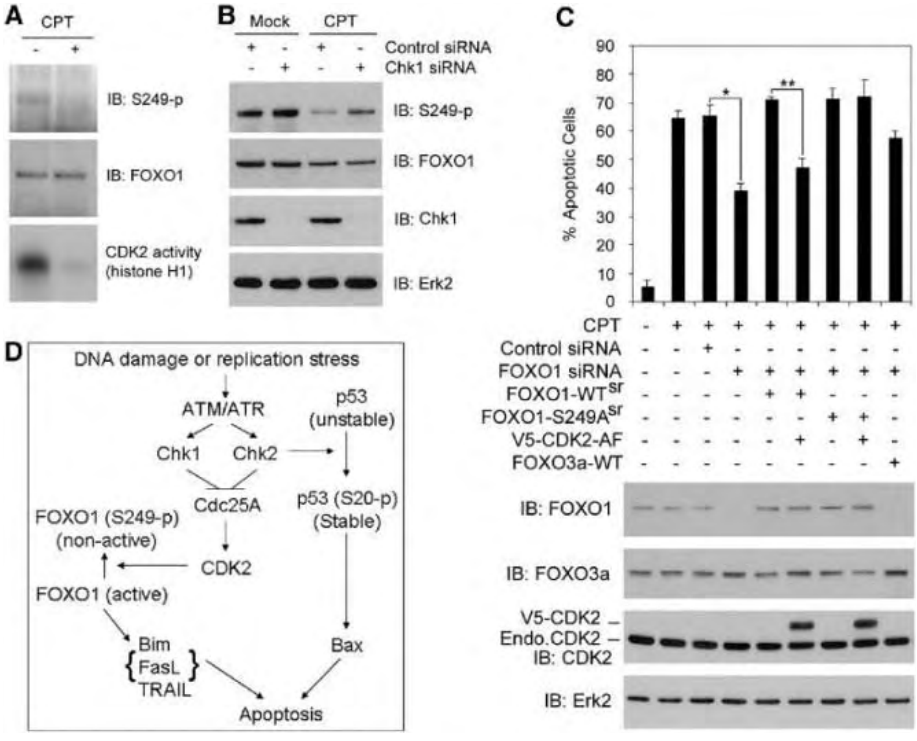

Fig. 4. Activation of FOXO1 is essential for cell death in response to DNA damage. (**A**) DU145 cells were treated with (+) or without (–) camptothecin (CPT) (1.25 μM). At 16 hours after treatment, endogenous FOXO1 proteins were subjected to immunoprecipitation (IP) with antibody to FOXO1 and immunoblotted (IB) with antibodies for Ser[249]-p and FOXO1. CDK2 activities were measured by in vitro kinase assays with histone H1 as substrate. (**B**) LNCaP cells were cotransfected with an expression vector of FLAG-FOXO1, a pool of Chk1-specific siRNAs, or a control siRNA. At 48 hours after transfection, cells were treated with CPT (1.25 μM) or mock-treated for 16 hours. Immunoprecipitation and immunoblotting were performed as in (A). Immunoblotting of Erk2 was used as a loading control. (**C**) DU145 cells were transfected with expression plasmids for enhanced green fluorescent protein as well as plasmids and siRNAs as indicated. At 24 hours after transfection, cells were sorted and replated in medium containing 2.5% of fetal bovine serum. At 24 hours after replating, cells were collected and immunoblotted for FOXO1 expression (top lane) or treated with CPT (1.25 μM). At 48 hours after CPT treatment, three sets of cells were analyzed for apoptosis (bar graphs). $*P = 0.002$; $**P = 0.0018$. Error bars indicate SD among three individual experiments. (**D**) Model of the role for CDK2-mediated phosphorylation and regulation of FOXO1 in the apoptotic response to DNA damage.

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Supporting Online Material

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Tissue Geometry Determines Sites of Mammary Branching Morphogenesis in Organotypic Cultures

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The treelike structures of many organs, including the mammary gland, are generated by branching morphogenesis, a reiterative process of branch initiation and invasion from a preexisting epithelium. Using a micropatterning approach to control the initial three-dimensional structure of mouse mammary epithelial tubules in culture, combined with an algorithm to quantify the extent of branching, we found that the geometry of tubules dictates the position of branches. We predicted numerically and confirm experimentally that branches initiate at sites with a local minimum in the concentration of autocrine inhibitory morphogens, such as transforming growth factor–β. These results reveal that tissue geometry can control organ morphogenesis by defining the local cellular microenvironment, a finding that has relevance to control of invasion and metastasis.

A burst of dichotomous and lateral branching at puberty transforms the mammary epithelial tubule rudiment present at birth into a fully elaborated ductal tree in the female adult. The overall process of branching morphogenesis is regulated globally by a number of cues, including growth factors, extracellular matrix (ECM) molecules, proteases, and morphogens (*1*–*4*). These global cues must be integrated locally within the context of the tissue to determine where branches are initiated; thus, a subgroup of epithelial cells is instructed to form a branch or to bifurcate, whereas neighboring cells are not (*5*). Current techniques to study this process, which is common to many organs including the lung, kidney, and salivary gland, do not allow for a precise quantitative understanding of how spatial positioning is determined. Given that the mammary ductal network branches out from preexisting epithelial tubules, we hypothesized that the position of cells within a tubule might provide contextual information to instruct branch site initiation.

To define the role of positional context, we developed a three-dimensional (3D) micropatterned assay for mammary epithelial branching morphogenesis that allowed us to mimic the mammary rudiment by controlling the initial geometry of tubules and to quantify the positions at which they branched. We engineered epithelial tubules of defined geometry by embedding functionally normal mouse mammary epithelial (EpH4) cells in cavities of collagen gel generated by molding unpolymerized collagen I around a patterned elastomeric stamp (Fig. 1A) (*6*). Embedded epithelial cells formed hollow tubules (*7*) conforming to the size and shape of the collagen cavities (Fig. 1, B and C, and fig. S1). To quantify branching and to represent its magnitude and position statistically, we stained nuclei and stacked multiple fluorescent images in registration such that the stacked image revealed the average spatial distribution of cells within, and branching from, the tubules (Fig. 1D). Stacked images were depicted as frequency maps (Fig. 1E) (*8*).

The tubules remained quiescent (Fig. 1E) until induced to undergo branching morphogenesis by addition of epidermal growth factor (EGF) (Fig. 1F) or hepatocyte growth factor (HGF) (fig. S1) (*9*). Within 24 hours after induction, multicellular branches extended into the surrounding collagen. These branches initiated only from the ends and not from the sides of the tubules (Fig. 1, F and G), a pattern reminiscent of the dichotomous branching of mammary end buds in vivo (*10*). Primary mammary epithelial cells or organoids formed correctly polarized bilayered tubules with myoepithelial cells and basement membrane surrounding an inner layer of luminal epithelial cells (Fig. 1H and fig. S1). Primary tubules also branched solely from the ends of the polarized bilayer (Fig. 1I).

To initiate a branch, cells must deform from their positions within the polarized epithelial tubule and must invade the surrounding tissue. Mammary and kidney epithelial cells in 3D cultures undergo a transient epithelial-to-mesenchymal transition (EMT) at the tips of branches as they invade the surrounding ECM

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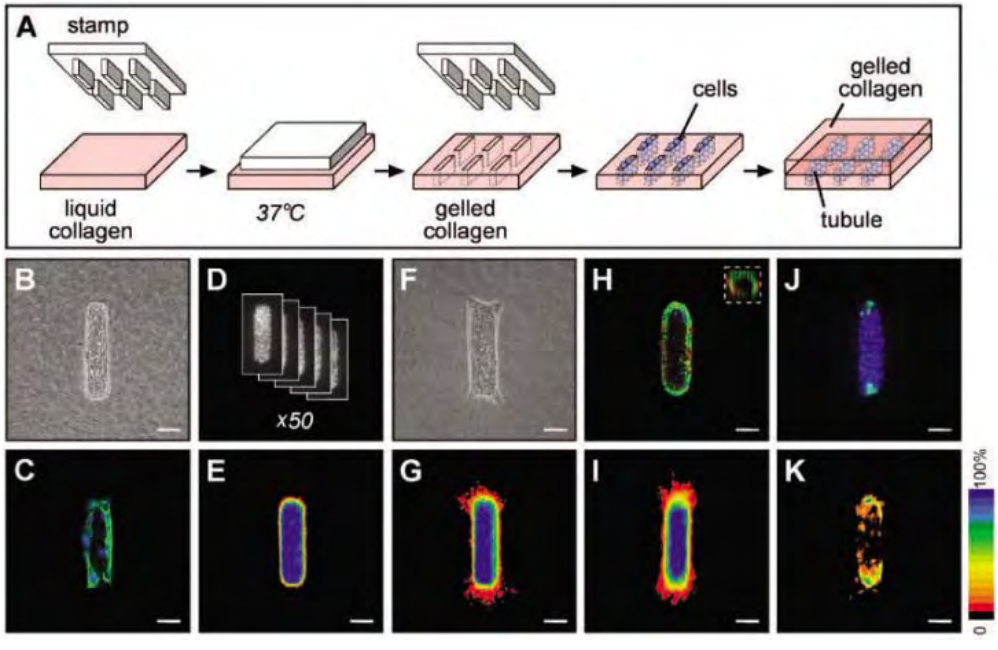

Fig. 1. Characteristics of branching from engineered mammary epithelial tubules. (**A**) Schematic of 3D microfabrication method to engineer tubules. (**B**) Phase contrast image and (**C**) confocal image of tubules stained for actin (green) and nuclei (blue) before induction of branching. The position of cells was quantified by (**D**) stacking images of nuclei from 50 tubules to generate (**E**) a frequency map before induction of branching. (**F**) Phase contrast image and (**G**) frequency map of tubules 24 hours after adding EGF to induce branching. (**H**) Confocal image of tubule of primary mammary epithelial cells stained for luminal epithelial keratin-8 (green), myoepithelial keratin-14 (red), and nuclei (blue); (inset) shows z section through tubule. (**I**) Frequency map of primary mammary epithelial tubules 24 hours after adding EGF. (**J**) Fluorescent image of vimentin gene promoter-GFP (green) and nuclei (blue) and (**K**) frequency map of vimentin gene promoter-GFP expression 8 hours after adding EGF. Scale bars, 50 μm.

(*10*–*13*). Because we could predict the position of branching with high certainty (~96 to 99%), we were able to determine whether acquisition of the invasive mesenchymal phenotype was restricted to these positions in the tubule before branch extension or merely correlated with the branches themselves. The appearance of mesenchymal attributes was assayed in situ in real time by monitoring expression of green fluorescent protein (GFP) under the control of the human vimentin gene promoter (*11*, *14*, *15*), and was found to be activated specifically in cells at positions that later branched (Fig. 1, J and K). Invasion during mammary branching morphogenesis requires matrix metalloproteinases (MMPs) and mesenchymally derived morphogens, such as epimorphin (*1*, *2*, *9*); blocking these activities prevented branching from the tubules, but did not prevent spatially localized activation of the vimentin gene promoter (fig. S2). These data reveal that the invasive phenotype is spatially restricted before extension of branches and that the cells are instructed to branch depending on their position within the tubule.

We confirmed that positional context controls branch sites by examining morphogenesis of tubules of varying geometry. Increasing the length of the tubules increased the magnitude of branching, although cells still branched exclusively from the ends (fig. S3). Curved tubules branched preferentially from the convex side of the curve (Fig. 2A). Asymmetric branching was also observed in bifurcated tubules and trees (Fig. 2, B and C), which preferentially branched from distal positions. The position of branching thus depended on the initial geometry of the tubule. Branching required cellular proliferation (fig. S4) (*9*), but the pattern of branching was not due to localized proliferation or locally enhanced signaling by growth factor receptors (fig. S4).

That branch sites depended on the initial tubule geometry suggested that positional context was encoded by the preexisting structure. Positional information during branching morphogenesis might be encoded by stimulatory morphogens secreted by adjacent mesenchymal tissues, which act as chemoattractants for growing epithelial branches (*4*, *16*). This mechanism would require an initial prepattern of signal within the mesenchyme. Alternatively, stimulatory cues released distally (such as the EGF or HGF, which we provided exogenously) might be balanced by inhibitory cues released locally by epithelial cells (*17*). In this scenario, branching would initiate only at tubule positions that were surrounded by a local minimum or subthreshold concentration of autocrine inhibitors. Because the epithelial cells within our engineered tubules exhibited patterned behavior in the absence of adjacent mesenchymal cells, we considered the possibility that branching position was determined by autocrine inhibitory morphogens secreted locally by the epithelial cells themselves.

To test this hypothesis, we generated a computational model of the concentration profile of hypothetical inhibitory molecules produced by epithelial cells in each of the engineered geometries by constructing a 3D model of diffusion. We assumed a constant flux (uniform rate of secretion) of inhibitors from the surface of the tubule and passive isotropic diffusion through the collagenous ECM. At steady state, a concentration gradient of inhibitors was found across each of the tubule geometries (Fig. 2, D to F, and figs. S1 and S3). Notably, the concentration of inhibitors was lowest in positions where branching was induced, in agreement with our hypothesis.

We thus investigated whether increasing the local concentration of inhibitors would be sufficient to block branching from the ends of tubules—regions that usually branched (Fig. 1G). One way to effect a local increase in inhibitor concentration is to decrease the distance between tubules (Fig. 3, A and B). Consistent with the predicted concentration profile, mammary epithelial cells branched from distant tubule ends, but not from ends near neighboring tubules (Fig. 3, C and D, and fig. S5). Varying the spacing between tubules revealed that branching was inhibited at distances up to ~75 μm (fig. S5); a similar ductal spacing is found in the mouse mammary gland (*18*). Therefore, inducing a change in concentration profile by altering the initial geometry of the tissue alters the position of branching.

A number of proteins inhibit mammary branching morphogenesis in vivo, including transforming growth factor–β (TGFβ) (*19*, *20*), which signals through a tetrameric complex of type I and type II receptors. Engineered tubules expressed TGFβ and its receptors (fig. S6), and immunofluorescence staining revealed a gradient in the concentration of TGFβ1 that correlated with our numerical predictions (Fig. 4A). Overexpression of active TGFβ1 completely inhibited branching (Fig. 4, B and C). To determine whether TGFβ acts as an endogenous inhibitor in this system, we used three approaches to disrupt its signaling: treatment with a function-blocking antibody against TGFβ1, treatment with a pharmacological inhibitor of TGFβ type I receptor kinase activity, and overexpression of a dominant negative TGFβ type II receptor. All treatments resulted in uniform branching from tubules of EpH4 or primary mammary epithelial cells (Fig. 4, D and E, and fig. S6), effectively abolishing the positional information.

These data demonstrate that tissue form and context—including the geometry of multicellular tubules, as well as their proximity to neighbors—can control the position of branching during

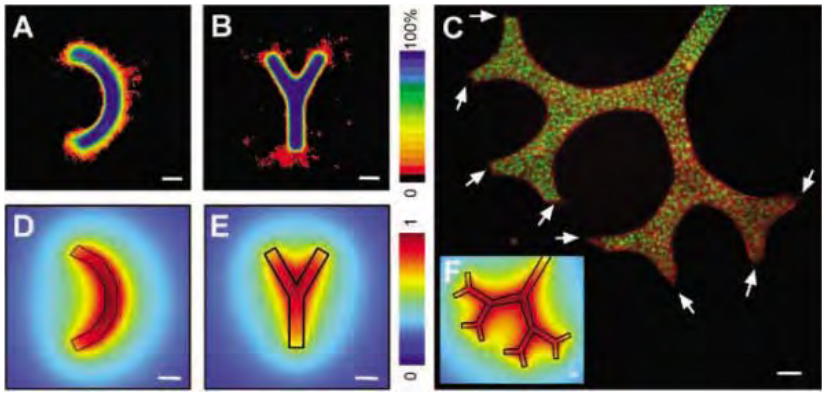

Fig. 2. Branching position is determined by tubule geometry and is consistent with the concentration profile of secreted diffusible inhibitor(s). Frequency maps 24 hours after induction of branching for (**A**) curved tubules, (**B**) bifurcated tubules, and immunofluorescence staining of actin (red) and nuclei (green) of (**C**) fractal trees. Branch sites in (C) are denoted by arrows; image stitched from multiple fields. Calculated concentration profiles of diffusible inhibitors for (**D**) curved tubules, (**E**) bifurcated tubules, and (**F**) fractal trees predict lowest local concentration of inhibitors where branching was found to be induced experimentally. Scale bars, 50 μm.

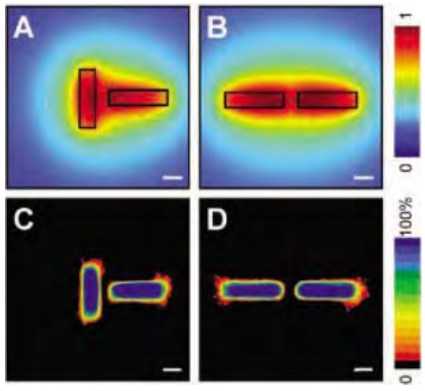

Fig. 3. Position of branching can be predicted by calculated concentration profile. Calculated profiles of diffusible inhibitors in tubules oriented perpendicular (**A**) and parallel (**B**) to each other. Frequency maps 24 hours after induction of branching confirm that branching is inhibited in regions predicted to be surrounded by a high concentration of inhibitors in perpendicular (**C**) and parallel (**D**) tubules. Scale bars, 50 μm.

morphogenesis of mammary epithelial cells and primary organoids. That this simple ex vivo system exhibits complex bifurcating and lateral branching behaviors suggests that the geometry of the duct may act as an instructive cue during its morphogenesis in vivo. This mechanism could explain how the mammary gland achieves its open architecture during development, a possibility to be explored further. We found that positional context is determined at least in part by the local concentration of autocrine TGFβ, an inhibitory morphogen in the mammary gland and other branched organs (*21*–*23*). Because TGFβ is secreted in an inactive latent form (*24*) and because overexpression of wild-type (latent) TGFβ1 had no effect on branching (fig. S6), we speculate that additional signals are required to sculpt the concentration profile of inhibitory activity that determines branching position. These signals may be chemical or mechanical in nature: MMPs and tissue inhibitors of MMPs (TIMPs) are known to affect branching (*1*, *2*, *25*), and intercellular tension can alter the response of cells to morphogens or the activity of morphogens themselves (*26*, *27*).

The balance between stimulatory and inhibitory morphogen gradients was postulated long ago by a number of theoretical scientists as a mechanism to explain pattern formation during development of other tissues (*28*–*30*). The model system presented here allows direct quantitative testing of the positional integration of these cues in a relevant developmental context and can be extended to investigate the mechanisms that control morphogenesis of any branched organ system.

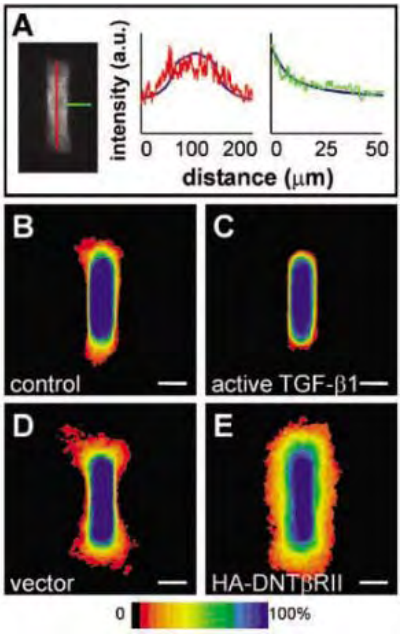

Fig. 4. Inhibitory activity is mediated in part by autocrine TGFβ in cultured cells. (**A**) Confocal section of primary mammary epithelial tubule stained for TGFβ1, with graphs representing relative pixel intensity (arbitrary units, a.u.) as a function of distance along tubules (red) and away from tubules (green). Numerical predictions are superimposed as solid blue curves to fit the intensity range. Frequency maps 24 hours after induction of branching in tubules of (**B**) control cells and (**C**) cells overexpressing active TGFβ1 confirm that TGFβ1 inhibits branching. (**D** and **E**) Positional control of branching is disrupted by blocking signaling of endogenous TGFβ1. Shown are frequency maps 24 hours after induction of branching in tubules of (D) vector control cells and (E) cells overexpressing dominant negative TGFβ receptor type II (HA-DNTβRII). Scale bars, 50 μm.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5797/298/DC1
Materials and Methods
Figs. S1 to S6
References

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Tandem Riboswitch Architectures Exhibit Complex Gene Control Functions

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Riboswitches are structured RNAs typically located in the 5′ untranslated regions of bacterial mRNAs that bind metabolites and control gene expression. Most riboswitches sense one metabolite and function as simple genetic switches. However, we found that the 5′ region of the *Bacillus clausii metE* messenger RNA includes two riboswitches that respond to *S*-adenosylmethionine and coenzyme B_{12}. This tandem arrangement yields a composite gene control system that functions as a two-input Boolean NOR logic gate. These findings and the discovery of additional tandem riboswitch architectures reveal how simple RNA elements can be assembled to make sophisticated genetic decisions without involving protein factors.

Many riboswitches are composed of two functional domains, an aptamer and an expression platform, that work in concert to selectively bind a target ligand and modulate gene expression (*1*–*3*). In nearly all examples identified in bacteria, binding of a single metabolite by the aptamer controls transcription termination or translation initiation via structural changes in the expression platform. Some riboswitches balance the kinetics of metabolite binding and RNA folding with the speed of RNA transcription to control gene expression appropriately (*4*–*6*). However, most metabolite-sensing RNAs are generally be-

lieved to be unsophisticated in structure and action compared with the diversity of gene control factors made of protein (*7*).

Some riboswitches are known to control gene expression by using complex structures and mechanisms. For example, *glmS* genes found in *Bacillus subtilis* and related bacteria are controlled by metabolite-responsive self-cleaving ribozymes (*8*, *9*). *glmS* ribozymes appear to use their target metabolite, glucosamine-6-phosphate, as a cofactor to accelerate mRNA cleavage (*10*, *11*). Another complex riboswitch class uses two aptamers in tandem to bind two glycine molecules cooperatively (*12*). Both glycine aptamers control gene expression by influencing the folding of a single intrinsic transcription terminator stem (*13*, *14*). This tandem aptamer assembly functions with far greater responsiveness to changing concentrations of ligand than do simple riboswitches.

Using filtered covariance model searches (*15*, *16*), we identified additional bacterial mRNAs that carry riboswitches or their substructures in tandem. The existence of these modular architectures implies that some bacteria are using RNAs to address more demanding gene control requirements. Of particular interest is the 5′ region of the *metE* gene from *Bacillus clausii*, which carries sequences and structures that conform to two known riboswitch classes that bind *S*-adenosylmethionine (SAM) (*17*–*19*) and coenzyme B_{12} (adenosylcobalamin or AdoCbl) (*20*, *21*) (Fig. 1A). This tandem riboswitch arrangement was detected in six different isolates of *B. clausii* with only modest nucleotide sequence differences [fig. S1, Supporting Online Material (SOM)], which indicates that the tandem SAM-AdoCbl riboswitch arrangement is important for this bacterial species.

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A rationale for the presence of two distinct riboswitches in the *metE* mRNA was established by examining the metabolic pathway for methionine biosynthesis (Fig. 1B and SOM). *B. clausii* can express two proteins (MetE and MetH) that independently catalyze the formation of methionine from homocysteine, as well as another protein (MetK) that converts methionine to SAM (Fig. 1B) (*22*). The mRNAs for all three proteins carry SAM riboswitches, which are extensively used by *Bacillus* and *Clostridium* bacteria to repress this pathway when SAM is plentiful (*17*–*19*, *23*). In contrast, only MetE expression should be reduced when AdoCbl is abundant (*24*, *25*), because cells can more efficiently produce methionine and SAM by expressing MetH, which requires the coenzyme methylcobalamin (MeCbl, a derivative of AdoCbl) (*24*–*26*).

The architecture of the *B. clausii* tandem SAM-AdoCbl riboswitch (Fig. 2A) suggests that the two ligands can independently repress *metE*. Each aptamer resides immediately upstream of a structure that resembles an intrinsic transcription terminator (*13*, *14*), and nucleotides known to be essential for ligand binding in both aptamers overlap with potential antiterminator stems. Thus, the *metE* tandem riboswitch arrangement is expected to function as a natural Boolean NOR logic gate (*27*), wherein either of two chemical inputs yields an output of gene repression.

NOR logic function does not require that the two riboswitches influence each other. To confirm that the tandem riboswitches function independently, we examined the metabolite-binding characteristics of a 405-nucleotide construct (405 *metE*) derived from the 5′ untranslated region (UTR) of the *B. clausii metE* mRNA (Fig. 2). 405 *metE* was subjected to in-line probing (*28*), which exploits the chemical instability of RNA to reveal ligand-induced changes in RNA structure (*1*). SAM causes substantial changes in spontaneous RNA cleavage amounts at locations residing only in the four-stem junction of the SAM aptamer (Fig. 2, A and B) (*19*). Likewise, AdoCbl causes modest structural changes exclusively in the AdoCbl aptamer (*20*, *21*) [see also (fig. S2)].

Independent function was confirmed by establishing dissociation constant (K_D) values for the binding of one ligand in the absence or presence of the other ligand (fig. S2). K_D values for each aptamer do not change significantly when the adjacent aptamer is saturated with its ligand (figs. S3 and S4). Moreover, binding profiles are consistent with a one-to-one interaction between RNA and each ligand. Therefore, the tandem aptamers do not bind ligands cooperatively, as is observed with some glycine riboswitches (*12*).

To establish transcription termination as the mechanism of riboswitch action, we examined metabolite-mediated changes in the levels of terminated and full-length transcripts. Transcription in vitro of a DNA construct encompassing the tandem riboswitches from *B. clausii metE* revealed that both ligands cause an increase in transcription termination relative to full-length transcripts (fig. S5) only at the two sites predicted to function as intrinsic transcription terminators (Fig. 2A).

Modulation of transcription termination in vitro is modest compared with similar in vitro transcription termination assays conducted with other riboswitches (*17*–*19*). Therefore, we conducted an analysis of mRNA transcript types in vivo to provide further evidence that SAM and AdoCbl induce transcription termination. Four sites within the *metE* RNA were targeted for qRT-PCR (quantitative reverse transcription–polymerase chain reaction) (*29*) with DNA primers that selectively amplify regions corresponding to the SAM (UTR-1) or AdoCbl (UTR-2) aptamers or to two different regions within the open reading frame (ORF-1 and ORF-2) (Fig. 3A). For quantification, we used samples of total RNA isolated from *B. clausii* cells grown in chemically defined medium (see SOM) alone or supplemented with either methionine or AdoCbl. Methionine supplementation is known to increase levels of SAM in bacteria (*30*) and has been used previously to regulate genes carrying SAM riboswitches (*19*).

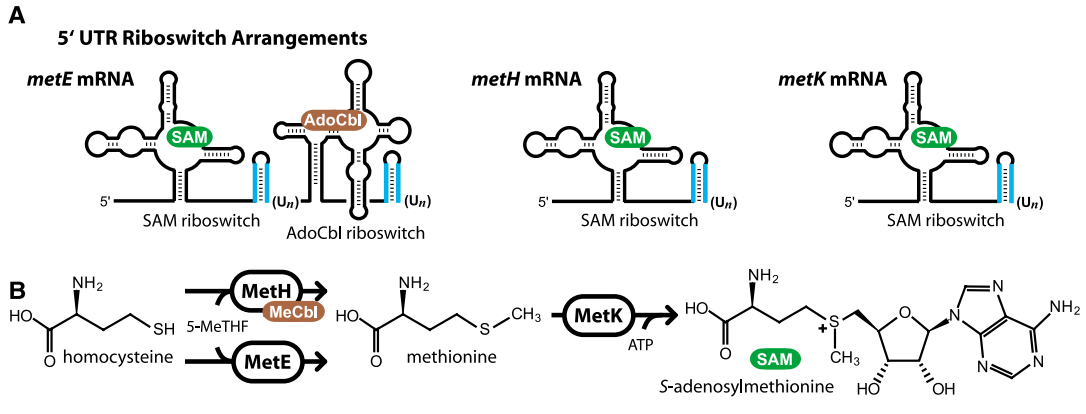


Fig. 1. Riboswitches reside adjacent to *B. clausii* genes encoding enzymes for the biosynthesis of methionine and SAM. (**A**) The *metE*, *metH*, and *metK* mRNAs carry riboswitches that are predicted to repress gene expression by transcription termination caused by formation of a stable RNA hairpin (light blue) followed by a run of six or more uridine nucleotides (U_n) (*13*, *14*). (**B**) Two different methionine synthase enzymes (MetE and MetH) independently convert homocysteine to methionine, and SAM synthase (MetK) converts methionine to SAM (*22*, *24*, *25*).

Selective amplification of ORF-2 of *metE* RNAs isolated under four growth conditions revealed substantial reductions in full-length transcripts when either compound was added to the medium, and an even greater decrease in full-length transcript abundance resulted when both compounds were added (Fig. 3B and fig. S6). These results suggest that both riboswitches control transcription termination and that both work independently.

A compilation of similar qRT-PCR data for the four amplified regions shows that there is a substantial shift from full-length to truncated transcript types under excess methionine or AdoCbl growth conditions (Fig. 3C and fig. S7). The progressive decrease in transcript abundance of RNAs that carry SAM, AdoCbl, and ORF regions is consistent with tandem ribo-

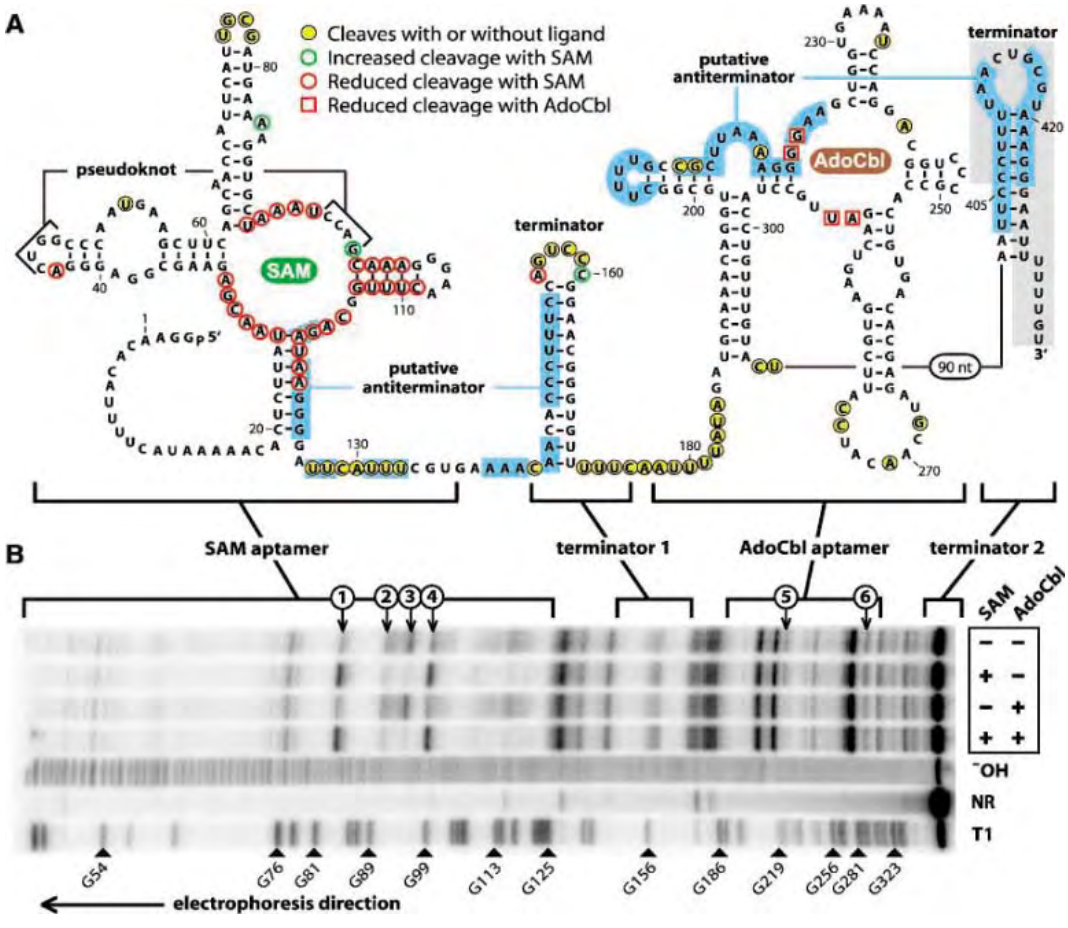
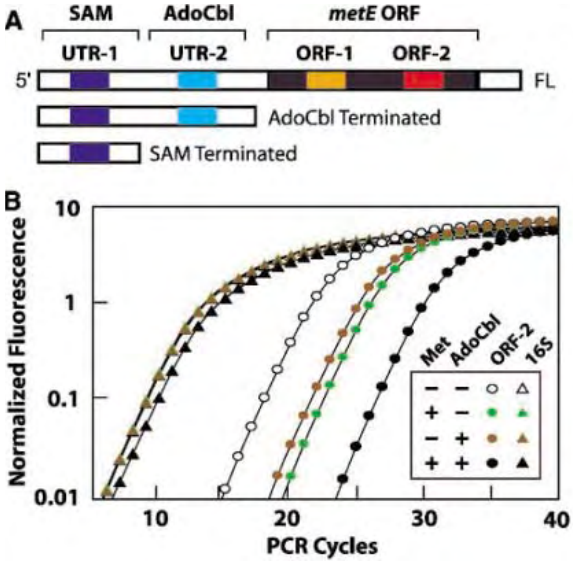


Fig. 2. The tandem SAM and AdoCbl riboswitches from the *B. clausii metE* mRNA independently bind their target metabolites. (**A**) Sequence and secondary structure models for riboswitches in the 5′-UTR of the *B. clausii* NRRL B-23342 *metE* mRNA. Nucleotides are numbered relative to the predicted natural transcription start site. The G residues at the 5′ terminus were included to aid efficiency of in vitro transcription by T7 RNA polymerase. Nucleotides not included in the 405 *metE* construct are boxed in gray. (**B**) In-line probing analysis (*28*) of 5′ ^{32}P-labeled 405 *metE* RNA. NR, T1, and ⁻OH identify rows containing nonreacted RNA, or RNA subjected to partial digest with ribonuclease T1 (G-specific cleavage) or alkali, respectively. Remaining lanes were incubated in the absence (–) or presence (+) of 10 μM SAM or 100 μM AdoCbl as indicated. Numbered arrows identify products of spontaneous RNA cleavage (analyzed in figs. S2 and S3) whose levels are altered in response to ligand-induced structural modulation.



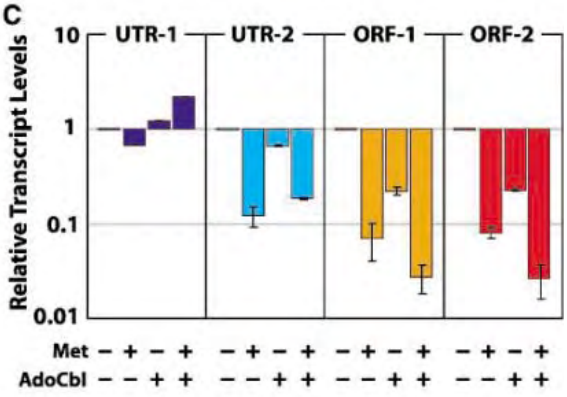


Fig. 3. Control of *metE* transcript length by tandem SAM and AdoCbl riboswitches from *B. clausii*. (**A**) Predicted *metE* transcript lengths and regions analyzed by qRT-PCR. FL designates full-length transcript (sections are not drawn to scale). (**B**) Representative qRT-PCR data for *metE* RNAs isolated from *B. clausii* grown with metabolite supplements as indicated. Amplification of region ORF-2 was monitored by detection of increasing SYBR Green fluorescence. A region of 16*S* RNA was amplified to confirm that equivalent amounts of RNA were used in each amplification. Some data points for 16*S* RNA quantification are obscured because of their similarity. (**C**) Plot of the relative amounts of *B. clausii metE* mRNAs of different lengths detected by qRT-PCR of four target sites using RNAs isolated under four growth conditions as indicated. A value of 1 reflects the level of mRNA measured when cells were grown without metabolite supplementation.

switches that act independently to terminate transcription on binding their corresponding ligands. Moreover, the vast majority of the changes in transcript abundance can be explained by riboswitch-mediated transcription termination without invoking other mechanisms such as transcription initiation or mRNA degradation.

We also investigated whether the metabolite-induced changes in relative abundance of transcript types corresponded to changes in protein expression. The complete *B. clausii metE* 5′ UTR was fused to a β-galactosidase reporter gene and integrated into the genome of *B. subtilis*. Reporter function was measured for cells grown in minimal medium, or in medium supplemented with methionine or AdoCbl (Fig. 4 and fig. S8). A construct carrying the wild-type tandem riboswitch yields a pattern of gene control that is consistent with NOR gate function. Some repression of the wild-type construct is expected in minimal medium, because the bacterial strains used for qRT-PCR and protein expression studies naturally synthesize methionine. Also, the AdoCbl concentration used for the in vivo assays was less than that needed for maximal repression to reduce interference of the compound's absorbance with the reporter signal (see SOM).

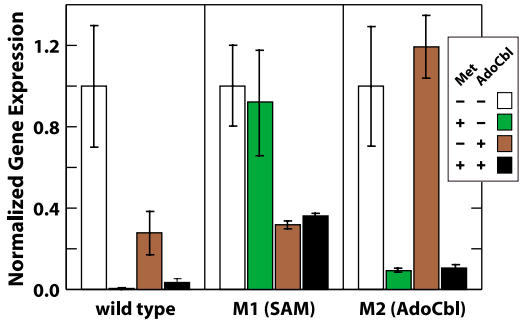


Fig. 4. Control of reporter gene expression by the tandem riboswitch arrangement exhibits NOR logic function. Plot depicts the level of gene expression for a β-galactosidase reporter gene fused to the 5′ UTR of the *B. clausii metE* mRNA or to two mutants that disrupt essential structures in the aptamers for SAM (M1; nucleotides 30 and 31 changed to A and G, respectively) and AdoCbl (M2; nucleotides 250 through 252 changed to UGG, respectively). β-Galactosidase activity (Miller units) measured in the absence of excess metabolites yielded 5.4 (± 1.6) for the wild-type UTR, 85.6 (± 17.0) for M1, and 15.8 (± 4.7) for M2.

Mutations that disrupt the consensus sequence or secondary structure of the SAM aptamer (M1) or the AdoCbl aptamer (M2) cause insensitivity to the corresponding ligands but do not affect the function of the adjacent unaltered riboswitch. These data support our conclusion that the *B. clausii metE* 5′ UTR carries two simple riboswitches that together permit protein production to be controlled by two different metabolites. At SAM and AdoCbl concentrations either well above or below those needed to trigger riboswitch action, the composite system operates as a genetic switch with Boolean NOR logic (*27*). Overall, this tandem riboswitch arrangement provides a capability that is similar to that found in

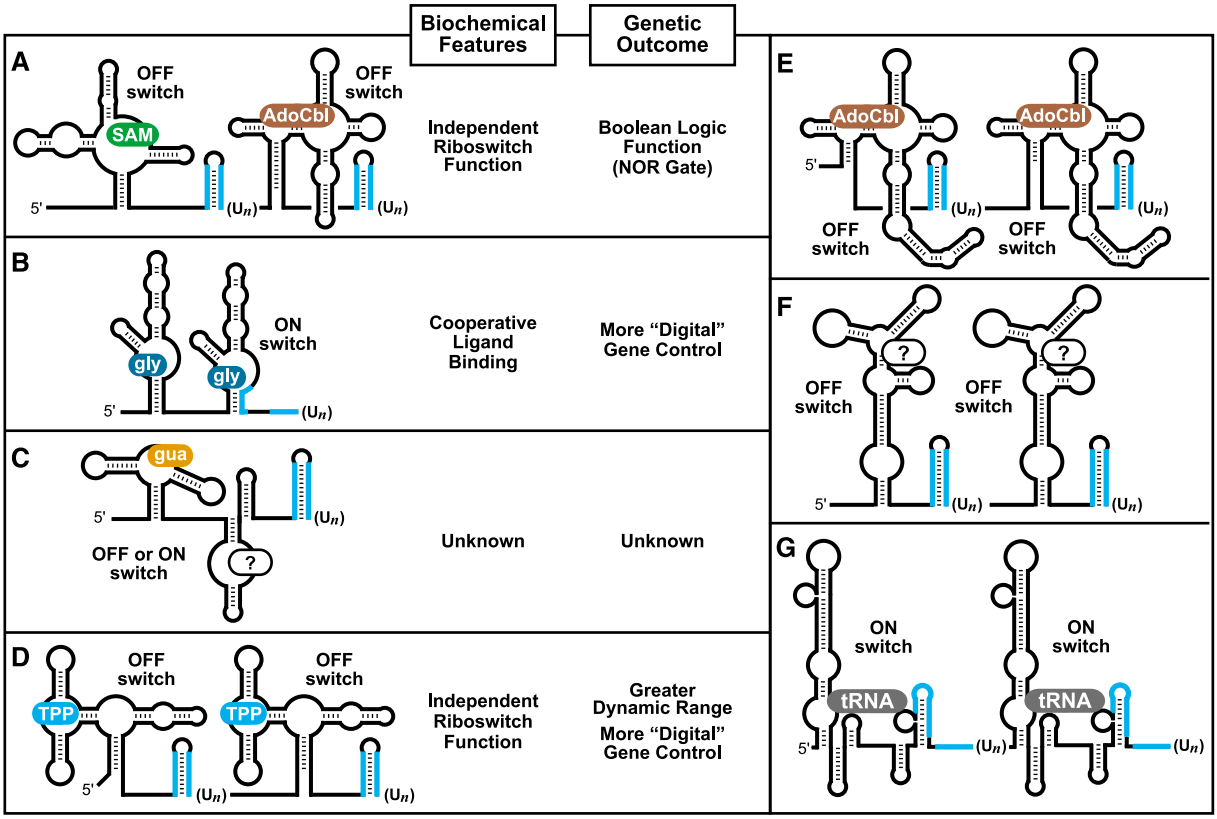


Fig. 5. Diverse tandem riboswitch configurations and functions. (**A**) Tandem SAM and AdoCbl riboswitches from the *B. clausii metE* mRNA described in this study. Transcription terminator stems are shaded light blue. (**B**) The common configuration of glycine (gly) riboswitches that carry two aptamers and one expression platform as observed with the *B. subtilis gcvT* mRNA (*12*). (**C**) Guanine (gua) aptamer (*33*) adjacent to a candidate riboswitch termed "*ykkC*" (*9*) with unknown ligand specificity as observed in the *Moorella thermoacetica purE* mRNA. (**D**) Tandem riboswitches for thiamine pyrophosphate (TPP) (*34*) found upstream of the *Bacillus anthracis tenA* gene, which is similar to a tandem TPP riboswitch arrangement reported previously (*36*). (**E**) Tandem AdoCbl riboswitches (*20*, *21*) found upstream of the *Desulfitobacterium hafniense* DSY1435 mRNA. (**F**) A tandem arrangement of a candidate riboswitch termed "*ykoK*" (*9*) found upstream of the *Bacillus halodurans mgtC* gene. (**G**) Tandem arrangement of T-box RNAs (*35*) as present in the *B. anthracis trpE* mRNA. Ligands whose identities are unknown are represented by (?). Experimental evidence supporting the proposed biochemical and genetic functions is reported for the architectures depicted in (A) (this study) and (B) (*12*).

Escherichia coli metE gene control (*31*, *32*). *E. coli* uses one protein factor to directly sense SAM and another protein factor that responds indirectly to AdoCbl (see SOM). The fact that these distantly related bacteria address the same complex gene control challenge with different polymers suggests that riboswitches are comparable to proteins in their function as metabolite-sensing gene regulators.

In addition to the NOR gate arrangement (Fig. 5A) described in this report and the cooperative glycine riboswitch (Fig. 5B) described previously (*12*), five other tandem riboswitch systems have been discovered. One new-found arrangement (Fig. 5C and fig. S9) includes a sequence and secondary structure that correspond to a guanine riboswitch aptamer (*33*) and a second element that is predicted (*9*) to function as a riboswitch aptamer for an unknown ligand. The architecture leads us to suggest that guanine binding would switch off expression and that the second ligand would switch on expression. Possible genetic outcomes are discussed in fig. S10.

The most common tandem arrangement discovered involves the presence of two complete riboswitches that respond to the same compound (Fig. 5, D to F). Tandem TPP riboswitches (*34*) from *Bacillus anthracis* (fig. S11) likely form a composite genetic switch that enables greater dynamic range for gene control and greater responsiveness to changes in metabolite concentration compared with lone riboswitches. In addition, it has recently been reported (*35*) that T-box RNAs, which activate gene expression by binding nonaminoacylated transfer RNAs, frequently occur in tandem (Fig. 5G).

It seems likely that additional tandem riboswitch arrangements will be identified that further expand the complex functions of metabolite-sensing RNAs. However, the current collection of tandem riboswitches already provides opportunities to establish how RNAs can be assembled in modular fashion to form complex gene control elements without relying on protein genetic factors.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5797/300/DC1
Materials and Methods
Figs. S1 to S11
References

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A Mutant Chaperone Converts a Wild-Type Protein into a Tumor-Specific Antigen

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Monoclonal antibodies have become important therapeutic agents against certain cancers. Many tumor-specific antigens are mutant proteins that are predominantly intracellular and thus not readily accessible to monoclonal antibodies. We found that a wild-type transmembrane protein could be transformed into a tumor-specific antigen. A somatic mutation in the chaperone gene *Cosmc* abolished function of a glycosyltransferase, disrupting O-glycan Core 1 synthesis and creating a tumor-specific glycopeptidic neo-epitope consisting of a monosaccharide and a specific wild-type protein sequence. This epitope induced a high-affinity, highly specific, syngeneic monoclonal antibody with antitumor activity. Such tumor-specific glycopeptidic neo-epitopes represent potential targets for monoclonal antibody therapy.

Tumor antigens expressed exclusively on the surface of cancer cells are ideal targets for monoclonal antibodies (mAb) because they are accessible, unlikely to have induced immune tolerance, and, when targeted, do not cause destruction of normal tissue (autoimmunity) (*1*). During tumor development, the host mounts humoral and cellular immune responses against the tumor (*2*). Serum from cancer patients contains high-affinity immunoglobulin G (IgG) antibodies specific for their own cancer cells but not reactive to non-neoplastic cells (*3*). However, the genetic origin and biochemical nature of many of these tumor-specific epitopes are incompletely understood (*4*). Many tumor-specific antigens result from somatic mutations that change the amino acid sequence, occur mostly in intracellular proteins, and are not readily accessible to antibodies (*5*). Few tumor-specific mutations have been identified in the extracellular domain of membrane proteins (*6*), and yet these are precisely the targets most likely to be visible to mAb.

Ag104A is a highly aggressive fibrosarcoma that arose spontaneously in an aging (female)

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mouse. 237 mAb (IgG2a)—a syngeneic, high-affinity mAb—shows exquisite specificity for Ag104A and does not react with a second spontaneous tumor (Ag104B) isolated from the same mouse, autologous non-neoplastic tissue (heart or lung fibroblasts, Ag104HLF), or any other tumor cell line tested (*7*, *8*). To identify the 237 mAb epitope, the antigen was purified from Ag104A cells by 237 mAb affinity chromatography and shown by amino acid sequencing to be OTS8, a sialomucin-like transmembrane glycoprotein of 172 amino acids also known as PA2.26, Aggrus, or T1alpha (*9*–*11*) (Fig. 1A). OTS8 is predominantly expressed by alveolar type I cells and overexpressed in murine and human tumors of various histologic origin (*11*). OTS8 is thought to be involved in tumor progression and invasion, but its exact biological function is still unknown. Using a rat mAb specific for OTS8, we confirmed that Ag104A indeed expressed OTS8, as did Ag104B, Ag104HLF, and other tumor cell lines known to express OTS8 (*12*) (Fig. 1B). However, of all the cell lines expressing OTS8, only Ag104A-OTS8 reacted with 237 mAb. Thus, 237 mAb was specific for a form of OTS8 found only in Ag104A. Immunoblotting of embryonic tissue and adult lung tissue showed OTS8 expression but no 237 mAb antigenicity (Fig. 1C). Thus, the 237 mAb epitope was not a differentiation or oncofetal antigen but truly tumor-specific.

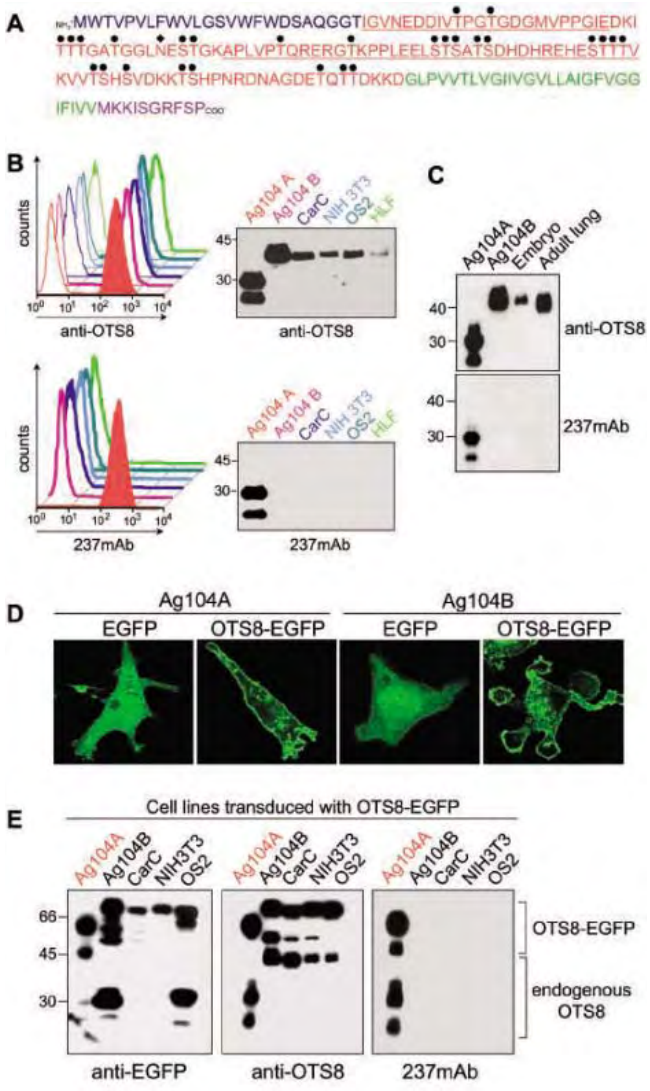

Fig. 1. 237 mAb showed absolute specificity to OTS8 expressed by Ag104A. (**A**) Amino acid sequence of OTS8; signal sequence (amino acids 1 to 24, blue), extracellular domain (ECD) (amino acids 25 to 134, red), transmembrane domain (amino acids 135 to 162, green), and the cytoplasmic region (amino acids 163 to 172, purple); OTS8-ECD contains one putative N-glycosylation site at Asn^{60} (◆) and 27 putative O-glycosylation sites (●). Peptide regions that were directly sequenced are underlined. (**B**) The 237 mAb recognized OTS8 expressed by Ag104A but not OTS8 expressed by other cell lines. Flow cytometric and immunoblotting of Ag104A and other cell lines for OTS8 expression and 237 mAb antigenicity. A rat IgG antibody was used as isotype control. (**C**) The 237 mAb antigen was not a differentiation or oncofetal antigen. OTS8 was highly expressed (45 kD) during embryogenesis (embryonic day 15) and in adult lung but did not show any reactivity to 237 mAb. Ag104A and Ag104B WCL were used as controls. (**D**) Confocal microscopy. OTS8-EGFP showed characteristic membrane distribution in both Ag104A and Ag104B, whereas unfused EGFP was diffusely localized. Single confocal planes (0.3 μm) are shown. Each panel is 65-μm wide. (**E**) 237 mAb bound to wild-type OTS8 in Ag104A. The cell lines used in (B) were retrovirally infected with pMFG OTS8-EGFP. Although the fusion protein was expressed in all cell lines as shown by anti-EGFP and anti-OTS8 immunoblotting, 237 mAb only recognized OTS8-EGFP in Ag104A WCL. OTS8 (endogenous and fusion protein) expressed in Ag104A had a molecular weight 15 to 20 kD lower than non-Ag104A OTS8.

To map the precise location of the carbohydrate epitope within the extracellular domain of OTS8 (OTS8 ECD), we developed a recombinant expression system (Fig. 2B). Regions of the OTS8 ECD were overexpressed in Ag104A as secreted His-tagged fragments and analyzed by 237 mAb immunoblotting. Fragments 25 to 75, 75 to 134, and 25 to 134 were expressed and secreted by Ag104A, but only 25 to 134 and 75 to 134 carried the antigenic carbohydrate epitope (Fig. 2B). Sequential addition of 10 amino acids to the 237 mAb-negative 25-to-75 fragment revealed that the epitope was located between amino acids 75 and 85 (Fig. 2B). This peptide, RGTKPPLEELS (*14*), harbors two potential O-glycosylation sites, Thr^{77} and Ser^{85}. Whereas Ser^{85}→Ala^{85} (S85A) and S85T point

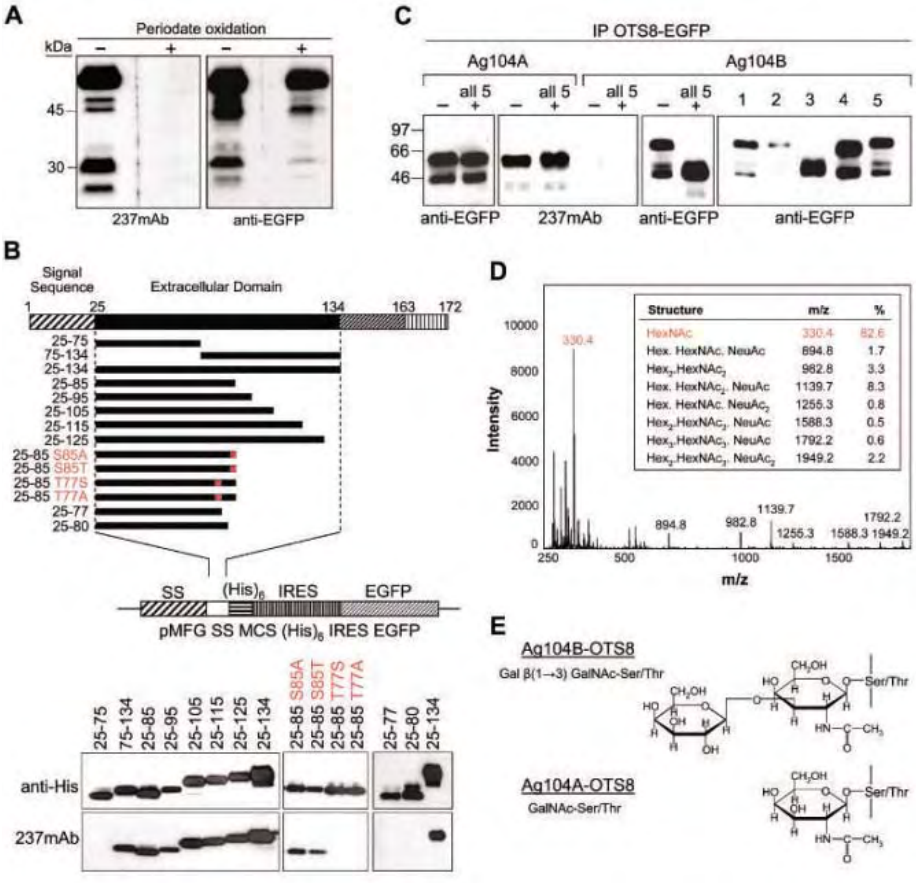

Fig. 2. Altered glycosylation of OTS8 created an antigenic carbohydrate moiety at amino acid Thr^{77}. (**A**) Oxidation of OTS8 carbohydrate groups with sodium periodate led to complete loss of 237 mAb immunoreactivity; the blots were reprobed with mAb to EGFP to confirm the presence of intact OTS8-EGFP protein. (**B**) Thr^{77} carried the antigenic carbohydrate moiety. Recombinant, His-tagged epitope fragments were cloned into pMFG single sequence (SS)–multiple cloning site (MCS)–(His)$_6$–internal ribosomal entry site (IRES)–EGFP for expression in Ag104A and analyzed by anti-His and 237 mAb immunoblotting. Point mutation of Thr^{77} to Ser or Ala led to loss of 237 mAb antigenicity. (**C**) OTS8 expressed in Ag104B was a sialylated Core 1 O-glycan, but Ag104A-OTS8 was not. Immunoprecipitated (IP) OTS8-EGFP from Ag104A and Ag104B was treated with a combination of five deglycosylating enzymes and assayed by anti-EGFP and 237 mAb immunoblotting. Lane 1, N-glycanase; lane 2, O-glycanase; lane 3, O-glycanase plus sialidase A; lane 4, sialidase A; and lane 5, β(1-4) galactosidase and glucosaminidase. Ag104A-OTS8-EGFP did not change in size or 237 mAb binding. Ag104B-OTS8-EGFP decreased 20 kD but still remained 237 mAb-negative after treatment with sialidase A plus O-glycanase. (**D**) Ag104A-OTS8 contained primarily GalNAc. Annotated matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrum of permethylated O-glycans was obtained by beta-elimination from Ag104A-OTS8. Shown are the mass-to-charge (m/z) values of selected peaks and relative quantity percentages (mass to mass) of the O-linked glycan structures. Hex, hexose; HexNAc, N-acetylhexose; NeuNAc, N-acetylneuraminic acid (also known as sialic acid). (**E**) Primary O-glycan carbohydrate structures present in OTS8 expressed in Ag104A and Ag104B. The normally glycosylated OTS8 carried mainly Core 1 structures; Ag104A-OTS8 contained predominantly GalNAc.

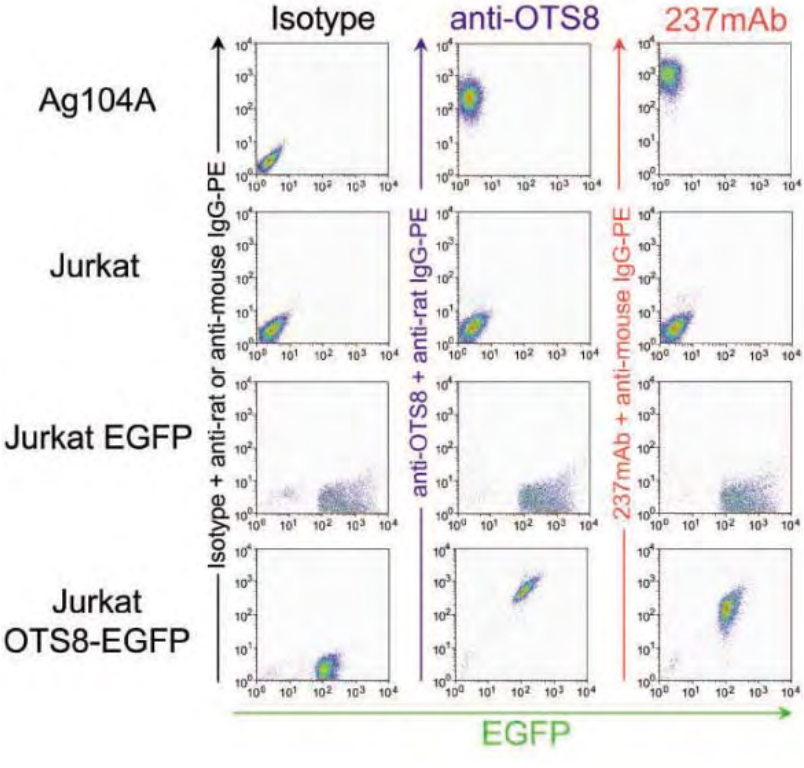

Fig. 3. The 237 mAb recognized a glycopeptidic epitope composed of GalNAc on Thr^{77} of OTS8. Flow cytometry of Jurkat, Jurkat EGFP, and Jurkat OTS8-EGFP for OTS8 expression and 237 mAb antigenicity. Although the parental Jurkat cells and Jurkat EGFP did not express OTS8 or the 237 mAb epitope, Jurkat OTS8-EGFP cells became positive for OTS8 expression and 237 mAb antigenicity; Ag104A was used as a control.

mutants remained 237 mAb-positive, T77A and T77S mutants were 237 mAb-negative (Fig. 2B); thus, the antigenic carbohydrate epitope was on Thr[77]. Given that 25 to 77 and 25 to 80 were 237 mAb-negative, amino acids 77 to 84 may have been needed for epitope creation and/or 237 mAb recognition (Fig. 2B).

We next compared the glycosylation profiles of nonantigenic OTS8 from Ag104B and antigenic OTS8 from Ag104A through enzymatic deglycosylation and found that nonantigenic OTS8 contained Core 1 [galactosyl-β(1-3)-*N*-acetylgalactosamine] with terminal sialic acid residues, whereas Ag104A-OTS8 did not (Fig. 2C). Carbohydrate analysis revealed that Ag104A-OTS8 contained primarily the monosaccharide *N*-acetylgalactosamine (GalNAc) (82%) (Fig. 2D and fig. S2). GalNAcα1-Ser/Thr, normally the precursor for longer O-glycans such as Core 1 (Fig. 2E), is also known as Tn antigen, an oncodevelopmental cancer–associated antigen frequently overexpressed on various cancers (*15*) and associated with several autoimmune diseases (*16*). Jurkat cells, a human T cell leukemia line known to express Tn (*17*), acquired 237 mAb antigenicity after being transduced to overexpress OTS8-EGFP (Fig. 3 and fig. S3). Thus, 237 mAb recognized a glycopeptidic epitope consisting of at most OTS8 amino acids 75 to 84 and GalNAc at Thr[77].

Because Ag104A contains GalNAc but no Core 1 structures, the normal addition of galactose to GalNAcα1-Ser/Thr was not occurring. The enzyme that catalyzes this linkage is Core 1 β1,3-galactosyltransferase (C1β3GALT) (*18*). In humans, C1β3GALT activity requires the coexpression of a molecular chaperone, Cosmc (Core 1 β3Gal-T–specific molecular chaperone) (*19*). A mouse gene (GenBank accession number NM_021550) that shows 91.5% homology to human *Cosmc* is X-linked (Xq23) and is predicted to encode a type II membrane protein of 316 amino acids (*20*). In Jurkat cells, a mutation in Cosmc leads to loss of C1β3GALT activity and ultimately to Tn overexpression (*19*). To examine whether defects in C1β3GALT or Cosmc could account for the abundance of Tn in Ag104A and subsequently for the creation of the 237 mAb epitope, C1β3GALT and Cosmc cDNA were sequenced. Whereas C1β3GALT cDNA did not have any mutations, Cosmc cDNA from Ag104A contained an in-frame deletion of nucleotides 509 to 587 predicted to delete 26 amino acids in the C-terminal region of the ECD (Fig. 4A). Cosmc cDNA from Ag104B and Ag104HLF was wild type, so the Ag104A-Cosmc deletion was somatic and tumor-specific. Sequencing of Ag104A genomic DNA did not show any wild-type Cosmc, suggesting a loss of heterozygosity at this locus (fig. S4). We reexpressed wild-type Cosmc in Ag104A to see if this would repair the defect in Ag104A. Notably, Ag104A cells that overexpressed wild-type Cosmc were 237 mAb-negative (Fig. 4, B and C), and OTS8 from these cells was the same size as Ag104B-OTS8 (Fig. 4C), indicating that it was now fully glycosylated. Moreover, we found that another spontaneous murine tumor, the neuroblastoma Neuro2A, also contained a Cosmc mutation resulting in Tn overexpression (fig. S5). Mutations that change amino acid sequence of a single protein create only one potential antigen, but the Cosmc mutation in Ag104A altered glycosylation globally on many cell surface proteins (fig. S6), creating many different possible glycopeptidic epitopes. Ag104A tumor-bearing mice developed Ag104A-OTS8–specific IgG (fig. S7), demonstrating the immunogenicity of aberrantly glycosylated OTS8, even in syngeneic hosts. mAb against such tumor-specific glycopeptidic epitopes can have therapeutic efficacy, as shown by the substantial anti-Ag104A activity of 237 mAb in vivo (fig. S8).

Qualitative and quantitative changes in O- and N-glycosylation are consistent features of malignancies (*21*–*23*). Thus, membrane proteins with aberrant carbohydrate moieties are logical targets for active and passive immunotherapy, and much effort and progress has been made to identify tumor-associated carbohydrate antigens (*22*, *23*) and glycopeptidic epitopes (*24*, *25*), to elucidate the mechanisms leading to their creation (*19*, *26*–*28*), and to augment their antigenicity and immunogenicity (*29*, *30*). Here, we found that a tumor-specific somatic mutation in a chaperone gene abolished the activity of a glycosyltransferase, disrupted O-glycan Core 1 synthesis, and ultimately created a glycopeptidic neo-epitope on a wild-type protein. The combination of a monosaccharide and a wild-type peptide sequence produced a tumor-specific antigen that induced the generation of a syngeneic, high-affinity mAb. Mutations in Cosmc have now been found in

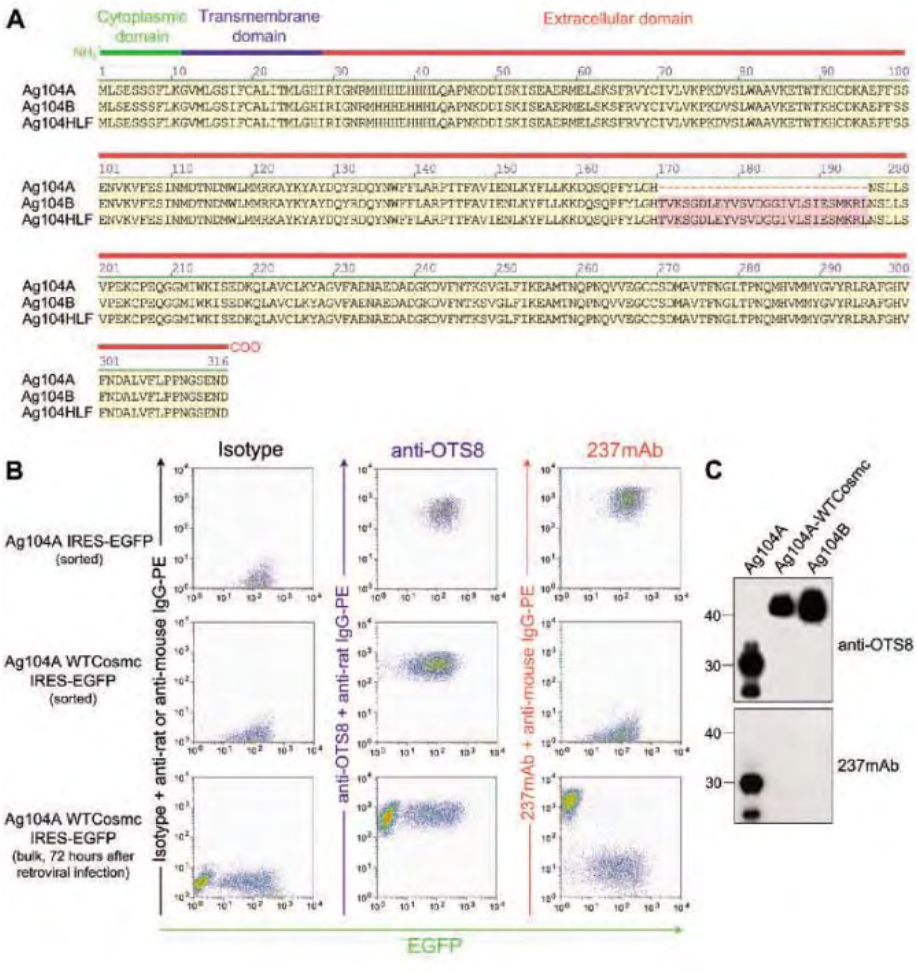

Fig. 4. An Ag104A-specific deletion mutation in the chaperone *Cosmc* led to creation of the 237 mAb epitope. (**A**) The predicted amino acid sequences of mouse Cosmc obtained from Ag104A, Ag104B, and Ag104HLF cDNA sequencing. Ag104A contained a deletion of nucleotides 509 to 587, resulting in the loss of 26 amino acids. (**B**) Repair of the mutation caused loss of the 237 mAb epitope. Ag104A was retrovirally infected with pMFG WTCosmc-IRES-EGFP (IE) or the control vector pMFG IRES-EGFP. Cells were analyzed by flow cytometry using an antibody to OTS8 or 237 mAb. Ag104A cells overexpressing WTCosmc expressed OTS8 but were 237 mAb-negative. (**C**) OTS8 from Ag104A WTCosmc–IRES-EGFP had the same molecular weight as Ag104B-OTS8 and was not recognized by 237 mAb.

multiple murine (Ag104A and Neuro2A) and human tumors (LSC, Jurkat) (*19*, *26*) and in patients with Tn syndrome (*16*), suggesting that this pathway may be commonly targeted in cancer cells, leading to the overexpression of Tn and subsequently to the creation of tumor-specific glycopeptidic neo-epitopes that can be targeted by mAb. The existing paradigm for tumor-specific antigen creation (from mutant gene to mutant protein to tumor antigen) must be expanded to include antigens generated by tumor-specific, posttranslational modifications of wild-type proteins.

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14. Single-letter abbreviations for the amino acid residues are as follows: A, Ala; C, Cys; D, Asp; E, Glu; F, Phe; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; P, Pro; Q, Gln; R, Arg; S, Ser; T, Thr; V, Val; W, Trp; and Y, Tyr.
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Herpes Simplex Virus Encephalitis in Human UNC-93B Deficiency

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Herpes simplex virus-1 (HSV-1) encephalitis (HSE) is the most common form of sporadic viral encephalitis in western countries. Its pathogenesis remains unclear, as it affects otherwise healthy patients and only a small minority of HSV-1–infected individuals. Here, we elucidate a genetic etiology for HSE in two children with autosomal recessive deficiency in the intracellular protein UNC-93B, resulting in impaired cellular interferon-α/β and -λ antiviral responses. HSE can result from a single-gene immunodeficiency that does not compromise immunity to most pathogens, unlike most known primary immunodeficiencies. Other severe infectious diseases may also reflect monogenic disorders of immunity.

HSV-1 is a widespread virus that infects about 80% of young adults worldwide (*1*). HSE is a rare complication of HSV-1 infection, first described in 1941 (*2*), but it is the most common type of sporadic viral encephalitis in western countries (about 1 patient per 250,000 person-years) (*3*, *4*). Mortality rates in HSE cases reached 70% before the advent of treatment with the antiviral drugs vidarabine in 1973 and acyclovir in 1981 (*5*). Most acyclovir-treated children survive, but many have neurological sequelae. The pathogenesis of this devastating viral illness is unclear, because it affects otherwise healthy patients. We hypothesized that HSE susceptibility may be inherited as a monogenic trait resulting in the specific impairment of immunity to HSV-1. This notion of pathogen-specific Mendelian immunodeficiency contrasts with the dominant paradigm, in which rare single-gene lesions confer vulnerability to multiple infections, whereas more common infections in otherwise healthy patients reflect polygenic predisposition (*6*). Consistent with our hypothesis, two related patients with HSE were reported in each of four unrelated families, with intervals of years between episodes affecting relatives in one or two generations (*7*–*10*). In addition, a recent genetic epidemiological survey of pediatric HSE in France reported a high frequency (13%) of affected consanguineous families [SOM text, note 1 (*11*)].

Most primary immunodeficiencies predispose subjects to multiple infectious diseases but not to HSE (*12*). However, two children with signal transducer and transcription activator (Stat-1) (*13*) and nuclear factor kappa B (NF-κB) essential modulator (NEMO) (*14*) deficiency were found to suffer from severe mycobacterial disease because of impaired IFN-γ–mediated immunity (*15*) and from HSE because of impaired interferon (IFN)-α/β– and -λ–mediated immunity (*16*). We therefore assessed IFN production by HSV-1–stimulated blood cells (*17*) from a series of otherwise healthy French children with sporadic HSE (SOM text, note 1). We detected two unrelated patients (P1 and P2), each born to first-cousin parents (SOM text, note 2). Both presented with HSE but showed no other evidence of unusual infectious disease and had efficiently controlled infections with at least nine viruses (SOM text, note 2). After 24 hours (fig.

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S1A) and 40 hours of HSV-1 stimulation, peripheral blood mononuclear cells (PBMCs) from these patients produced markedly lower levels of IFN-α and IFN-β, and marginally lower levels of IFN-λ than control cells from 50 healthy individuals (Fig. 1, A and B, and fig. S1B). However, these PBMCs produced normal levels of IFN-γ (Fig. 1A), tumor necrosis factor (TNF)–α, interleukin (IL)–1β, and IL-6 (fig. S1C). IFN-α (Fig. 1C), -β, and -λ (fig. S1, D and E) production in response to 10 other viruses (except possibly encephalomyocarditis virus) was also impaired. Blood leukocyte subsets—including IFN-producing dendritic cells (*18*–*21*)—were, however, present in normal numbers (fig. S1F).

Virus detection and IFN-α/β and -λ production by PBMCs may be mediated by surface-expressed Toll-like receptor 4 (TLR4) and, to a greater extent, intracellular TLR3, TLR7, TLR8, and TLR9, which can be triggered by nucleic acids mimicking viral products (*17*, *22*, *23*). The patients' cells responded normally to lipopolysaccharide (LPS), an agonist of TLR4, in terms of IFN-β and -λ mRNA production and the secretion of other cytokines (Fig. 1D and fig. S1G). However, these cells showed impaired IFN-α, -β, and -λ, IL-1β, TNF-α, and IL-6 production in response to all specific agonists of TLR7 (3M-13, R-848), TLR8 (3M-2, R-848), and TLR9 (CpG-C) tested (Fig. 1E and fig. S1G). Cells from both patients showed normal IFN and cytokine responses to the nonspecific TLR3 agonist polyinosinic-polycytidylic acid [poly(I:C)] under culture conditions, in which all control cells responded (Fig. 1, E and F, and fig. S1, G to I). Finally, the patients responded well to IL-1β and other TLR agonists (except possibly the TLR5 agonist flagellin, like some healthy controls) (Fig. 1G and fig. S1J) and to TNF-α (Fig. 1H). The two patients with HSE therefore had defects in their response to TLR7, TLR8, and TLR9 stimulation (not formally excluding the possibility of impaired TLR3 and TLR5 activation).

The cellular responses of the two patients resembled that described for mice lacking UNC-93B, an endoplasmic reticulum protein with 12 membrane-spanning domains involved in TLR3, TLR7, and TLR9 activation (TLR8 is absent in mice, and TLR5 response was not tested in mutant mice) (*24*). P1 was found to be homozygous for a four-nucleotide deletion (CTTT) at positions 1034 to 1037 in *UNC93B1* exon 8 (1034del4) (Fig. 2A and fig. S2A) (*25*). P2 was homozygous for a single-nucleotide substitution at position 781 (G>A), the last nucleotide of exon 6 (781G>A). Full-length *UNC93B1* mRNAs from P1 and P2 were barely detectable by reverse transcription polymerase chain reaction (Fig. 2B), and an alternatively spliced mRNA, lacking exon 6, was found in P2 (fig. S2B). Neither of the mutant alleles carried by P1 and P2 were found in a survey of 100 healthy European controls. The patients'

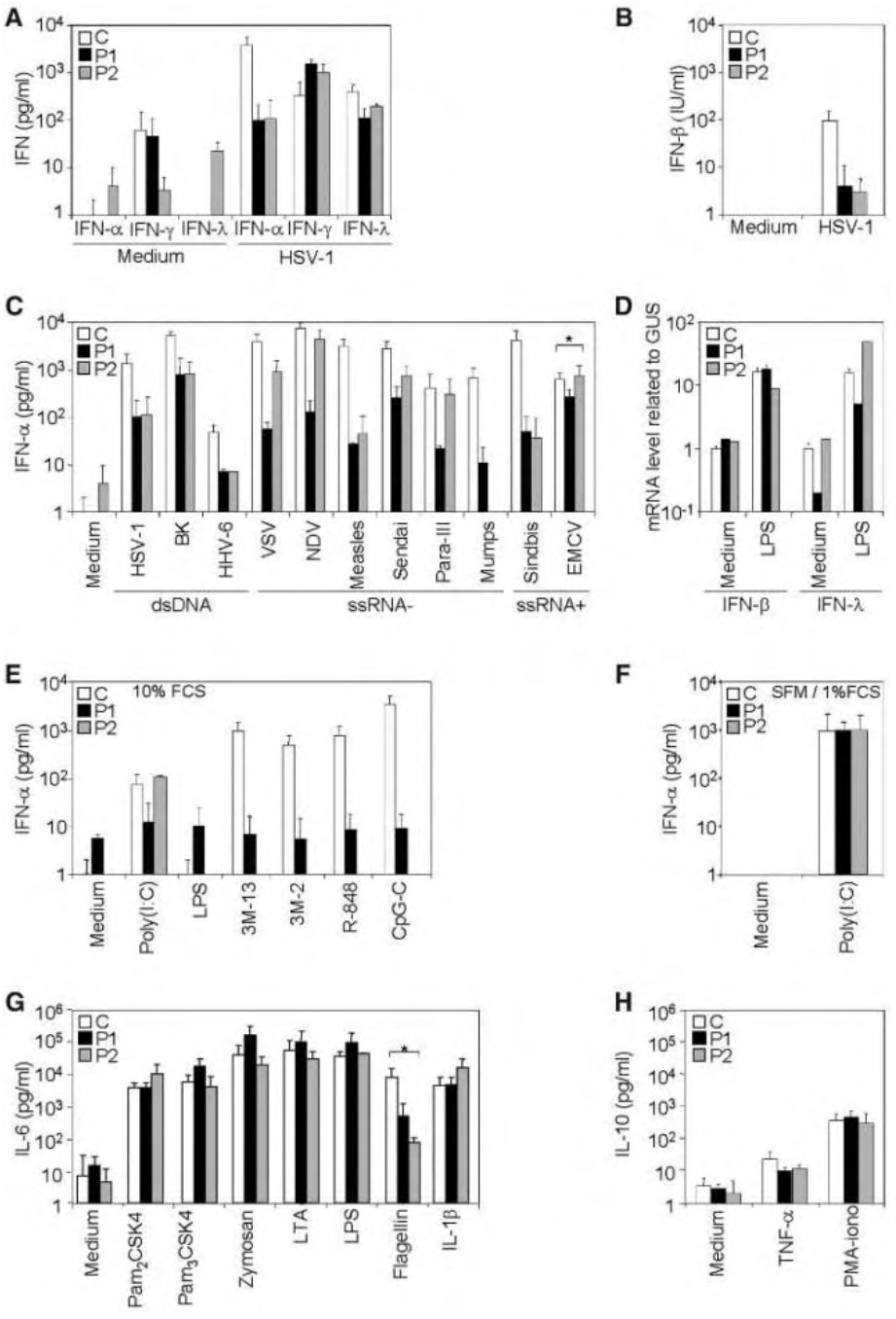

Fig. 1. Impaired IFN-α, -β and -λ production by blood cells in response to viruses and TLR7, TLR8, and TLR9 agonists. (**A** and **B**) IFN-α, -β, -γ and -λ production in PBMCs left unstimulated or stimulated with HSV-1 for 40 hours and tested by enzyme-linked immunosorbent assay (ELISA). (**C**) IFN-α production by PBMC, assessed by ELISA, 40 hours after stimulation with intact viruses [see (*11*) for multiplicity of infection (MOI) values]. P2 was tested only once for human herpesvirus 6 (HHV-6). (**D**) IFN-β and -λ mRNA levels in PBMC, unstimulated or stimulated for 2 hours with LPS. β-glucuronidase (GUS) was used for calibration. Two experiments were carried out for P1 and a single experiment for P2. (**E**) IFN-α production, measured by ELISA, in PBMC in RPMI supplemented with 10% fetal bovine serum (FBS), in response to poly(I:C) (TLR3), LPS (TLR4), 3M-13 (TLR7), 3M-2 (TLR8), R-848 (TLR7/8), and CpG-C (TLR9), 40 hours after stimulation [see (*11*) for concentrations]. (**F**) IFN-α production in PBMC in serum-free medium (SFM) or in RPMI supplemented with 1% FBS, in response to poly (I:C). (**G**) IL-6 production, assessed by ELISA, in response to Pam_2CSK4 (TLR2/6), Pam_3CSK4 (TLR1/2), zymosan (TLR2/6), lipoteichoic acid (LTA) (TLR2), LPS (TLR4), flagellin (TLR5), and IL-1β, 24 hours after whole-blood stimulation [see (*11*) for concentrations]. (**H**) IL-10 production, assessed by ELISA, in response to TNF-α and phorbol-myristate-acetate-ionomycin, 24 hours after whole-blood stimulation. For experiments indicated with an asterisk (*), the mean values for each patient and control values were not significantly different. All comparisons were performed on log-transformed values. Experiments (A to C and E to H) were carried out at least thrice for P1 and twice for P2. Mean values ± SD are indicated.

parents and siblings who were tested were heterozygous for the corresponding mutant alleles (Fig. 2C); their cells responded normally to R-848, vesicular stomatitis virus (VSV), and HSV-1 (Fig. 2D and fig. S2C), and they did not develop HSE upon HSV-1 infection. The 1034del4 and 781G>A alleles were thus recessive for both clinical (HSE) and immunological (lack of viral and TLR responsiveness) phenotypes, strongly implicating UNC-93B deficiency as the probable cause of HSE in these two patients.

Human skin–derived fibroblasts express TLR3 and respond to poly(I:C) (*26*). Moreover, the nonresponsiveness of fibrosarcoma cell line P2.1 to poly(I:C) results from TLR3 deficiency (*27*). We thus studied fibroblasts from P1 and showed that they failed to produce IFN-β and IFN-λ in response to poly(I:C), HSV-1, or VSV (Fig. 2E and fig. S2D) but responded well to TNF-α. The impaired fibroblast response to poly(I:C) contrasted with the normal response of the patient's blood cells, probably reflecting the strict TLR3 dependence of the poly(I:C) response in fibroblasts and the use of TLR3-independent pathways in PBMCs. This is consistent with the role of mouse UNC-93B in the TLR3-dependent response to poly(I:C) of peritoneal macrophages (*24*). We then used the patient's fibroblasts to validate the pathogenic role of the mutant *UNC93B1* alleles. Upon transient transfection with a wild-type *UNC93B1* allele, but not with mock vector, P1 fibroblasts regained normal IFN-β and IFN-λ secretion in response to poly(I:C) (Fig. 2F and fig. S2E). Similarly, P1 fibroblasts stably transfected with a wild-type *UNC93B1* allele regained the ability to produce IFN-β upon VSV infection (fig. S2F). These complementation studies confirmed that the *UNC93B1* mutant alleles were responsible for the impaired fibroblast responses to both poly(I:C) and viruses.

We further characterized the impact of UNC-93B deficiency by studying the responses to poly(I:C) in fibroblasts from P1 and a patient with interleukin-1 receptor–associated kinase (IRAK)–4 deficiency [with resulting impaired responses to IL-1β and agonists of TLR7, TLR8, and TLR9, but not TLR3 agonist poly(I:C) (*17*, *28*)]. Poly(I:C) failed to induce the production of *IFN*β and *IFN*λ mRNAs in P1 cells (fig. S3A), and dimerization of the intracellular viral response protein interferon regulatory factor (IRF)–3, mitogen-activated protein kinase (MAPK) p38 phosphorylation (fig. S3, B and C), and the DNA-binding activity of NF-κB (fig. S3D) were impaired. In P1 cells, NF-κB and MAPK p38 were activated normally in response to IL-1β and TNF-α. We then tested the response of Epstein-Barr virus (EBV)–transformed B cells to TLR7 and TLR8 agonists (*17*). With each of the cytokines examined, including IFN-α, -β, -γ, and -λ, only TNF-α was reproducibly induced in all control EBV-B cells after stimulation with the TLR7/8 agonists 3M-2, 3M-13, and R-848. Unlike control cells, those from P1 and the IRAK-4–deficient patient failed to secrete TNF-α (fig. S3E) and did not show the normal degradation of IRAK-1 in response to TLR7/8 stimulation (fig. S3F). Human UNC-93B is thus involved in the response to TLR3, TLR7, and TLR8 agonists and operates upstream from IRF-3, NF-κB, MAPK, and IRAK-1.

Finally, we explored the pathogenesis of HSE in the UNC-93B–deficient patients by investigating the possible role of this protein

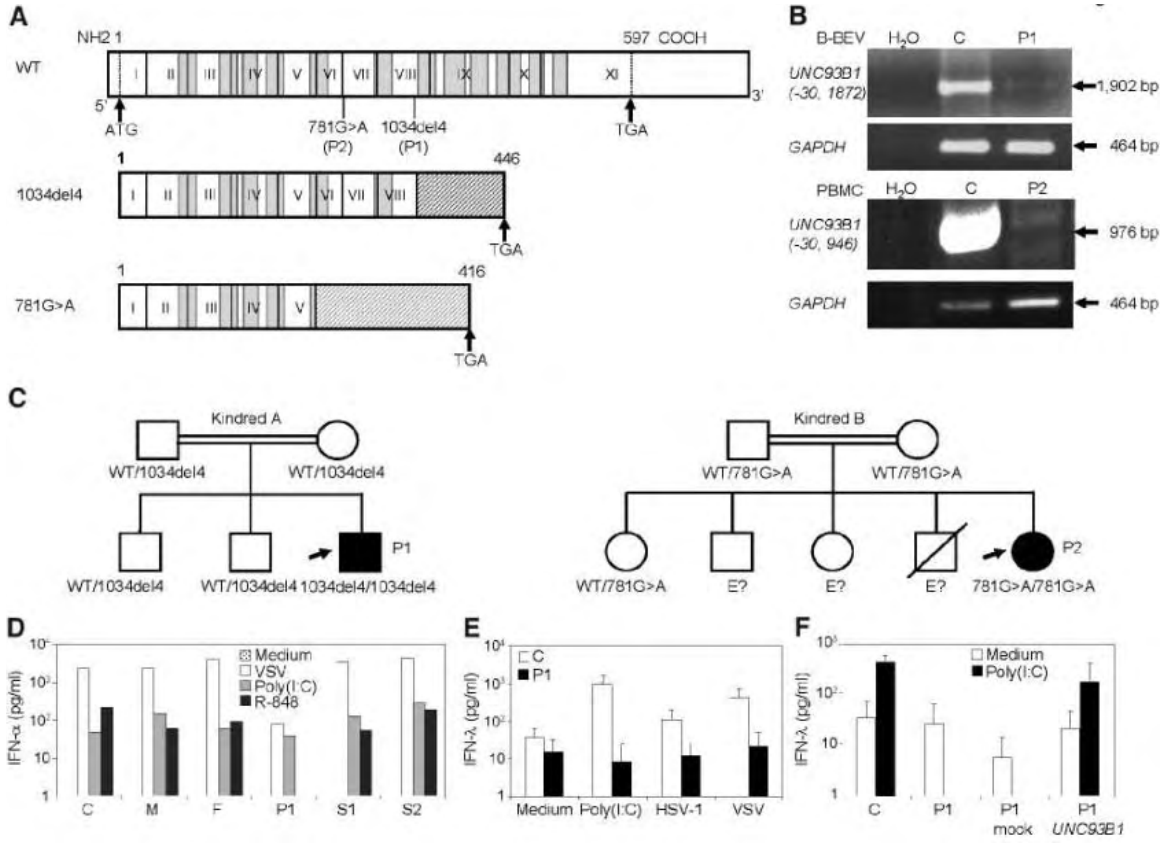

Fig. 2. Autosomal recessive UNC-93B deficiency and impaired fibroblastic cell responses to viruses and TLR3 agonist. (**A**) Schematic representation of *UNC93B1* gene structure. Human *UNC93B1* has 11 exons (Roman numerals), encoding a protein with 12 predicted transmembrane domains (shown in gray). 1034del4 (P1) results in a frameshift that creates a premature stop codon in exon 9 at position 1339–1341. 781G>A (P2) generates an alternatively spliced mRNA, lacking exon 6, and the resulting frameshift creates a premature stop codon in exon 9 at position 1249–1251. (**B**) *UNC93B1* cDNA in an EBV-transformed B cell line from a healthy control (C) and P1, after full-length PCR amplification. The internal amplification control was *GAPDH*. A shorter *UNC93B1* cDNA product is shown for PBMC from C and P2. (**C**) Family pedigrees, with allele segregation in two families. The patients, in black, are homozygous for the mutation. All other family members tested, in white, are heterozygous. (**D**) IFN-α production, assessed by ELISA, in PBMC from P1 and his mother (M), father (F), and siblings (S1 and S2), in response to 40 hours of stimulation with VSV, poly(I:C), and R-848. (**E**) IFN-λ production, measured by ELISA, in SV40-transformed fibroblast lines from a control (C) and P1, upon stimulation with poly(I:C), HSV-1, or VSV for 24 hours. (**F**) IFN-λ production, measured by ELISA, in SV-40–transformed fibroblast lines from a control (C) and P1, upon stimulation with poly(I:C) for 18 hours [see (*11*) for concentrations]. The patient's fibroblasts were tested 48 hours after transient transfection, with an insertless vector (mock) or a pCDNA3 expression vector containing the wild-type *UNC93B1* cDNA. Mean values ± SD are indicated.

in the cell-autonomous control of viruses. Four hours after infection, UNC-93B– and Stat-1–deficient (*13*) fibroblasts sustained remarkably high rates of VSV replication (Fig. 3, A and B). Most control cells remained alive 24 hours after infection, whereas the rates of cell death for UNC-93B– and Stat-1–deficient cells increased similarly with viral titer (Fig. 3C). Similar results were obtained with HSV-1, which is less cytopathic and induces IFN less strongly than VSV in human fibroblasts (Fig. 3D). Thus, UNC-93B–deficient and Stat-1–deficient cells derived from patients displaying vulnerability to HSE displayed high rates of cytolysis after viral infection. However, in UNC-93B–deficient cells treated with recombinant IFN-α2b before viral infection, the cellular phenotype was fully complemented in terms of both viral titer (Fig. 3E) and cell viability (Fig. 3, F and G). Thus, the higher level of cell death in UNC-93B–deficient cells was a consequence of enhanced viral growth, itself resulting from impaired IFN-α/β production upon viral infection. These findings for fibroblasts may extend to neurons, providing a plausible pathogenic mechanism for HSE, but do not exclude the possible involvement of hematopoietic cells involved in antiviral immunity.

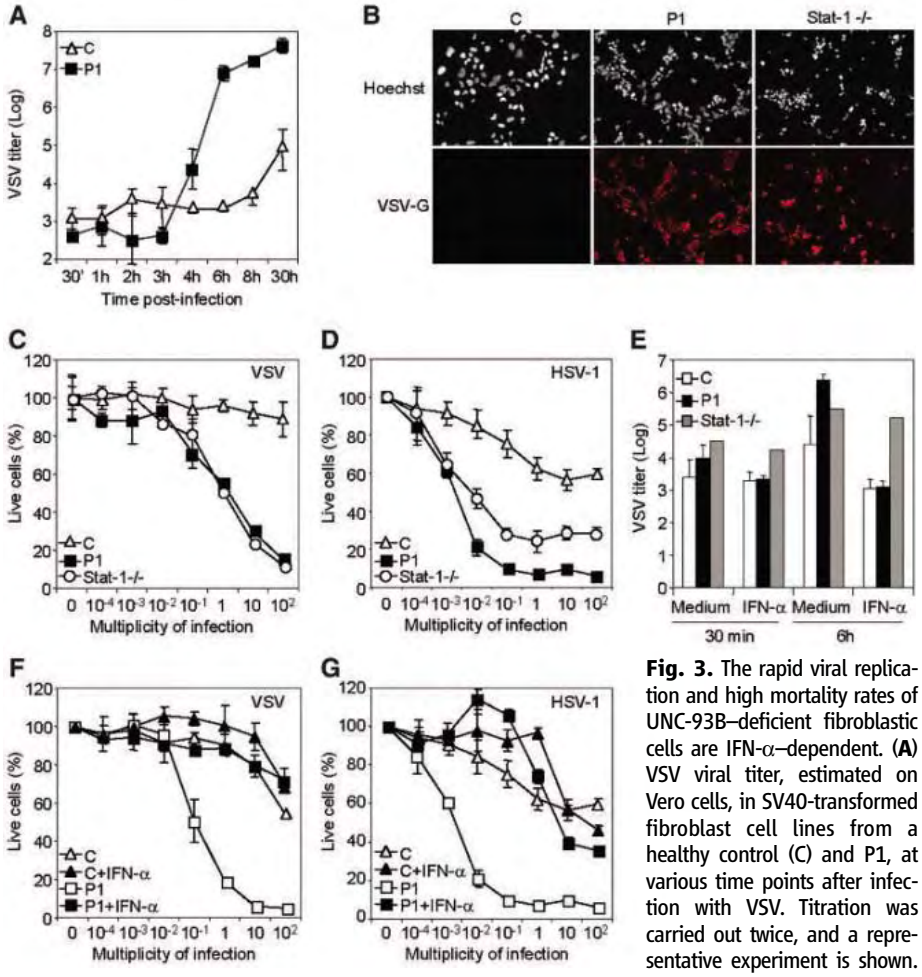

Fig. 3. The rapid viral replication and high mortality rates of UNC-93B–deficient fibroblastic cells are IFN-α–dependent. (**A**) VSV viral titer, estimated on Vero cells, in SV40-transformed fibroblast cell lines from a healthy control (C) and P1, at various time points after infection with VSV. Titration was carried out twice, and a representative experiment is shown. (**B**) Intracellular VSV-G protein levels in SV40-transformed fibroblast cell lines from a healthy control (C), P1, and a Stat-1–deficient patient (Stat-1$^{-/-}$) 5 hours after infection with VSV. This experiment is representative of three, with two different SV40-transformed control fibroblast cell lines. Nuclei were stained with Hoechst stain. (**C** and **D**) Live cell percentage, estimated by resazurin oxidation/reduction, for SV40-transformed fibroblast cell lines from a healthy control (C), P1, and a Stat-1–deficient patient (Stat-1$^{-/-}$), 24 and 96 hours after infection with various MOI of VSV (C) and HSV-1 (D), respectively. (**E**) VSV viral titer, estimated on Vero cells, for SV40-transformed fibroblast cell lines from a healthy control (C), P1, and a Stat-1–deficient patient (Stat-1$^{-/-}$), 30 minutes and 6 hours after infection. Fibroblast cells were used untreated or after treatment with recombinant IFN-α2b 18 hours before infection. (**F** and **G**) Percentage of live cells, estimated by resazurin oxidation/reduction, for the SV40-transformed fibroblast cell lines from a healthy control (C) and P1, 24 and 96 hours after infection with various MOI of VSV (F) and HSV-1 (G), respectively. Fibroblast cells were used untreated or after treatment with recombinant IFN-α2b 18 hours before infection. Mean values ± SD are indicated.

We have identified autosomal recessive UNC-93B deficiency as a genetic etiology of HSE in otherwise healthy patients. We have previously shown that the human TLR7-, TLR8-, and TLR9-IFN-α/β and -λ signaling pathways are IRAK-4–dependent and redundant for immunity to most viruses, including HSV-1 (*17*). Our findings thus indicate that the UNC-93B–dependent production of IFN-α/β and -λ controls HSV-1 by TLR3-dependent and/or TLR-independent pathways. Unexpectedly, UNC-93B appears to be redundant for protective immunity to most other microbes, including viruses. UNC-93B–deficient mice were susceptible to multiple infections under experimental conditions (*24*), whereas our patients with HSE, infected under natural conditions—the hallmark of the human model (*29*)—were otherwise healthy. This discovery broadens our view of primary immunodeficiencies, which should no longer be seen as restricted to children with multiple infectious diseases (*6*). Severe infectious diseases in the general population do not necessarily reflect complex genetic predisposition but may show Mendelian inheritance (*30*). Finally, our results have important therapeutic implications, as at least some HSE patients would probably benefit from recombinant IFN-α treatment, as suggested by mouse models of HSE (*31*), just as patients with mycobacterial disease and genetic defects resulting in low endogenous IFN-γ levels benefit from life-saving IFN-γ treatment (*15*).

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A Small Microbial Genome: The End of a Long Symbiotic Relationship?

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Intracellular bacteria are characterized by genome reduction. The 422,434–base pair genome of *Buchnera aphidicola* BCc, primary endosymbiont of the aphid *Cinara cedri*, is ~200 kilobases smaller than the previously sequenced *B. aphidicola* genomes. *B. aphidicola* BCc has lost most metabolic functions, including the ability to synthesize the essential amino acid tryptophan and riboflavin. In addition, most retained genes are evolving rapidly. Possibly, *B. aphidicola* BCc is losing its symbiotic capacity and is being complemented (and might be replaced) by the highly abundant coexisting secondary symbiont.

Genome reduction in endosymbiotic bacteria is a continuous process derived from their adaptation to intracellular life. One unsolved question is whether reduction reaches a threshold, or if it is an ongoing process that inevitably leads to bacterial extinction and replacement by a new symbiont. Current debate centers on whether genomic streamlining is a result of deletion bias or natural selection, and has implications for the theory of genome complexity evolution (*1*). The obligate association between aphids and their maternally transmitted intracellular symbiont *Buchnera aphidicola* offers a model system to analyze genome reduction and its consequences. Genome sizes ranging from 450 to 641 kb have been reported in *B. aphidicola* strains from different aphid subfamilies, with the genome of *B. aphidicola* from the aphid *Cinara cedri* (*B. aphidicola* BCc) being the most dramatically reduced (*2*). A particular feature of *C. cedri* is the presence of large numbers of a secondary symbiont (*3*), "*Candidatus* Serratia symbiotica" (*S. symbiotica*) (*4*).

The genome comparison of three previously sequenced *B. aphidicola* strains (*5*–*7*) showed almost total conservation of genome architecture since their last common symbiotic ancestor. Selective gene losses in the extant lineages appear to be mainly related to host-specific properties (*6*, *7*).

The *B. aphidicola* BCc genome is composed of a 416,380–base pair (bp) circular chromosome plus a 6045-bp plasmid for leucine biosynthesis (tables S1 to S3) (*8*, *9*). Gene loss, scattered along the chromosome (fig. S1), is the main cause of genome shrinkage, because there is no reduction in the sizes of intergenic regions and open reading frames. With only 362 protein-coding genes, this genome represents the minimal known gene set able to support cellular life.

Gene loss affects all functional categories (figs. S1 and S2; table S4), although not evenly. Genes necessary for RNA metabolism (transcription and translation) are the most preserved, representing 35% of the genome's coding capacity. The DNA replication machinery is also complete, but the repair machinery is further reduced than in other strains. Chaperone systems and all essential components for protein translocation are also well preserved, ensuring proper folding and positioning of membrane protein components. These include a highly simplified flagellar apparatus, composed only of those elements homologous to the type III virulence secretion system required for the invasion of the host cells (*10*).

Gene losses affecting biosynthesis of nucleotides, cofactors, cell envelope, and transport are particularly acute. Hence, *B. aphidicola* BCc depends entirely on its host for nucleotide and cofactor provisioning. In addition, and in contrast to what has been described in other strains (*11*), *B. aphidicola* BCc is clearly unable to provide riboflavin to its host. Finally, it lacks most of the transporters encoded by other *B. aphidicola* genomes. Because it has also lost all the genes for aminosugar and peptidoglycan biosynthesis, it appears that *B. aphidicola* BCc must be close to a free-diffusing cell, in which most metabolites can be passively exchanged through a highly simplified cell envelope.

The putative *B. aphidicola* BCc metabolism inferred from the extant genes (fig. S3) is reduced simply to using glucose to obtain energy through substrate-level phosphorylation, plus the production of saturated fatty acids and all the essential amino acids, except tryptophan. All genes encoding the adenosine 5′-triphosphate synthase subunits have been lost, indicating that the retained components of the electron transport chain must be involved in the regeneration of nicotinamide adenine dinucleotide for glycolysis and acetyl–coenzyme A biosynthesis. In the absence of all genes necessary for the biosynthesis of phospholipids, the preservation of the complete saturated fatty acid pathway indicates that *B. aphidicola* BCc, and *B. aphidicola* in general, probably provide them to the host.

Aphids, like other animals, require adequate quantities of 10 essential amino acids that are lacking in their diet and must be provided by their endosymbionts. *B. aphidicola* BCc has retained the biosynthetic capacity for all essential amino acids except tryptophan. The importance of tryptophan production by the endosymbiont has been experimentally demonstrated (*12*), and the close relative *B. aphidicola* BCt, endosymbiont of the aphid *Cinara tujafilina*, possesses *trpE and trpG* (the two regulatory genes of the tryptophan pathway) on a plasmid (*9*). *C. cedri* and *C. tujafilina* are almost identical (*13*), and their plant hosts are also very similar. Yet, *B. aphidicola* BCt contains the genes for tryptophan biosynthesis whereas *B. aphidicola* BCc has lost the complete pathway, which suggests that *B. aphidicola* BCc is not only unable to provide tryptophan to its host, but must obtain it from another source. Although secondary symbionts are considered facultative in other aphids, *S. symbiotica* is present in all the *C. cedri* clones we have worked with. They are always contained within well-defined bacteriocytes, are present at a density similar to that of *B. aphidicola* (Fig. 1;

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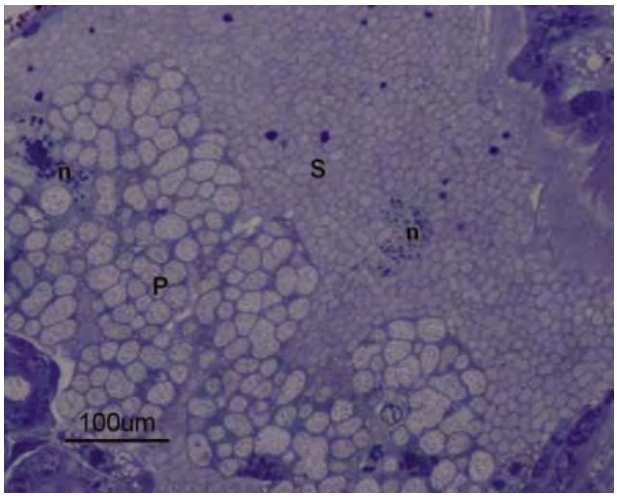

Fig. 1. Microscopic analysis of *C. cedri* bacteriocytes. Semi-thin section showing two types of bacteriocytes, identifiable by their different tonality with toluidin blue. P, primary symbiont (*B. aphidicola*); S, secondary symbiont (*S. symbiotica*); n, bacteriocyte nuclei.

fig. S5), are located in the central part of the bacteriome, and are surrounded by primary bacteriocytes (*3*). The polymerase chain reaction amplification and sequencing of a *trpE* fragment from *S. symbiotica* (*8*) indicate that this symbiont synthesizes tryptophan and supplies it to the whole symbiotic system.

The evolution of *B. aphidicola* BCc sequences appears to have been particularly rapid. In general, the ratio of synonymous to nonsynonymous substitutions, *dN*/*dS*, of *B. aphidicola* protein-coding genes is higher than those of free-living bacteria, owing to an accelerated rate of nonsynonymous substitution (*14*). This pattern is more marked in *B. aphidicola* BCc (*8*) (table S5). Tests of the relative accumulation of nucleotide substitutions performed for all possible *B. aphidicola* strain pairs (table S6) revealed that the *B. aphidicola* BCc branch accumulates a significantly higher number of substitutions in most of its genes (table S7). The genes with higher *dN*/*dS* ratios are not associated with any particular functional role (fig. S4). Finally, we analyzed the type of selection that operates on protein-coding genes in *B. aphidicola* (table S8). Most of the genes are under purifying selection ($dS > dN$), but about 12% of the genes are under neutral selection in *B. aphidicola* BCc ($dS = dN$), as expected for pseudogenes.

Taking together all functional, evolutionary, and microscopic data, we postulate that *B. aphidicola* BCc is undergoing a process of genome degradation and functional replacement by the coexisting *S. symbiotica* (*3*). Natural symbiont replacement of *B. aphidicola* by a fungus was postulated to have occurred in aphids of the tribe Cerataphidini (*15*), whereas experimental evidence of secondary symbionts taking on the role of *B. aphidicola* has been demonstrated in infection experiments of *B. aphidicola*–cured aphids (*16*). All the analyses performed point to a more extreme gene-degradation effect occurring in the *B. aphidicola* BCc genes than in other *B. aphidicola* lineages. Indeed, the loss of most DNA-protecting and DNA-repair mechanisms in *B. aphidicola* BCc, more so than in the other *B. aphidicola* lineages, would enhance the mutation rate. Further, *B. aphidicola* BCc has apparently lost its role as a tryptophan and riboflavin supplier to its host and indeed cannot even supply its own needs, which must be provided by *S. symbiotica*, not only to the host but also to *B. aphidicola* BCc. Thus, the mutualistic relationship between *B. aphidicola* and its aphid host seems to have taken on a new, more complex role that includes a second endosymbiont and might end up in a replacement.

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17. Financial support was provided by projects BFM2003-00305 from "Ministerio de Ciencia y Tecnología" (MCyT) and "ACOMP06/251" from "Generalitat Valenciana," Spain. We acknowledge the sequencing facility at the Servei Central de Suport a la Investigació Experimental (Universitat de València) for sequencing support. V.P.-B. is a recipient of a fellowship from the "Ministerio de Educación, Cultura y Deporte," Spain. R.G. is a recipient of a contract in the "Ramón y Cajal" Program from the MCyT, Spain. We thank J. Peretó, R. Gross, and F. J. Ayala for valuable comments on the manuscript. The GenBank accession numbers are CP000263 for the chromosome and AY438025 for pLeu.

Supporting Online Material

www.sciencemag.org/cgi/content/full/314/5797/312/DC1
Materials and Methods
SOM Text
Figs. S1 to S5
Tables S1 to S8
References

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(discussion leaders are italicized)

AGRICULTURAL SCIENCE
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
MAR 11-16, 2007
KEN FELDMANN &
WILHELM GRUISSEM, CO-CHAIRS
DWIGHT TOMES &
ROBERTO TUBEROSA, CO-VICE CHAIRS

- **High Impact Achievements in Agriculture**
  (*Phil Dale* / John Bennett / Pam Ronald / Bruce Tabashnik / Rob Horsch)
- **Leading Agricultural Biotechnology in China**
  (*Qifa Zhang* / Longping Yuan / Jiayang Li / Jikun Huan)
- **Leading Agricultural Biotechnology in Europe**
  (*Ralph-Michael Schmidt* / Patrick Schweizer / Markus Frank / Ian Graham)
- **Translational Genomics - Moving from Model Plants to Crops**
  (*Rod Wing* / Mike Bevans)
- **Plants and Human Health - Improving Crops for Developing Countries**
  (*Paul Anderson* / Peter Beyer / Joe Thome / Jonathon Gressel / Richard Sayre)
- **Novel Approaches to Abiotic and Biotic Stress in Crop Plants**
  (*Roberto Tuberosa* / Cory Christensen / William Niebur / Ralph Panstruga / Jian-Kang Zhu)
- **Transgenes and Epigenetics in Agriculture**
  (*Marja Timmermans* / Mark Cigan / Steve Jacobsen / Milo Aukerman / Graham Moore / Olivier Voinnet)
- **Energy Crops Biotechnology - Meeting the Needs of Tomorrow**
  (*Ken Vogel* / Michael Casler / Joseph Bouton / Gautam Sarah)

ANTIMICROBIAL PEPTIDES
IL CIOCCO
LUCCA (BARGA), ITALY
APR 29-MAY 4, 2007
YLVA ENGSTROM & YECHIEL SHAI, CO-CHAIRS
RICHARD GALLO & PAUL MCCRAY, JR., CO-VICE CHAIRS

- **More Than Two Decades of Antimicrobial Peptides: Where Are We?**
  (*Ylva Engström* / *Yechiel Shai* / Tom Ganz / Jules A. Hoffmann)
- **Regulation of Antimicrobial Peptides**
  (*Bob Lehrer* / Robert L. Modlin / Marc R. Ackermann / Jonathan J. Ewbank)
- **Conventional and Non-Conventional Functions of AMPs**
  (*Michael Zasloff* / Alan M. Krensky / Andre J. Ouellette / Paul Martin)
- **Synthetic Antimicrobial Peptides and Mimetics**
  (Samuel H. Gellman / Charles M. Deber / Amram Mor / John A. Robinson)
- **Host-Pathogen Interaction at Epithelial Surfaces**
  (*Birgitta Agerberth* / Annelie Brauner / Henk P. Haagsman / Mona Bajaj-Elliott)
- **Recognition of Bacteria, Pathogenesis and Microbial Resistance**
  (*Eduardo A. Groisman* / Victor Nizet / Dan Hultmark / Gregory B. Martin)
- **Moving AMPs from Bench to Application**
  (*Hans-Henrik Kristensen* / Lars Steinstraesser / Michael S. Verlander)
- **Mode of Action of AMPs**
  (*Hans-Georg Sahl* / Burkhard Bechinger / Richard M. Epand)
- **Evolution of Innate Immunity and AMPs**
- **Hot Corner I: New Results - Controversial Issues - New Methods**
  (*Richard L. Gallo* / *Paul B. McCray*)
- **Hot Corner II: Late Breaking News - New Concepts in Innate Immunity**
  (*Robert E. Hancock*)

BIOGENIC HYDROCARBONS & THE ATMOSPHERE
CROWNE PLAZA
VENTURA, CA
FEB 25-MAR 2, 2007
CHRIS GERON & NICK HEWITT, CO-CHAIRS
PAOLO CICCIOLI &
JOSE FUENTES, CO-VICE CHAIRS

- **Global Importance and Research Priorities** (*Rainer Steinbrecher* / Alex Guenther / Parvadha Suntharalingam)
- **Biosynthesis of BVOCs and their Emission Processes** (*Ray Fall* / Claudia Vickers / J.-P. Schnitzler / Ulo Niinemetz)
- **Atmospheric Chemistry of BVOCs: Science and Policy Implications** (*Paul Shepson* / Spyros Pandis / Betty Pun)
- **Biological Interactions and the Ecological Roles of BVOCs** (*Josep Penuelas* / Guy Poppy / Jonathan Gershenzon / Ben Moore)
- **Early Career Scientists - Isoprene: Emission Controls and Chemistry** (*Jose Fuentes* / Neil Donahue / Alona Linatoc / Mick Wilkinson / Jesse Kroll / Malcolm Possell / Amy Wiberly)
- **Biogenic Hydrocarbons and the Global Atmosphere** (*Hanwant Singh* / Paul Palmer / Piero DiCarlo / Armin Hansel / Yoshizumi Kajii)
- **Early Career Scientists - BVOC: Analytical Techniques to Inventories** (*Russ Monson* / Nicole Bouvier / Jeanie Tsui / Levi Mielke / Deanne Grant / Jun Zhao / Thomas O'Halloran)
- **Biogenic VOCs in a Changing World** (*Francesco Loreto* / David Stevenson / Jian Hui Bai / Paulo Artaxo / Barbara Turpin)
- **Future Directions** (*Tom Sharkey* / Todd Rosenstiel / Almut Arneth)

CAG TRIPLET REPEAT DISORDERS
CENTRE PAUL LANGEVIN
AUSSOIS, FRANCE
MAY 13-18, 2007
DIANE MERRY, CHAIR
JANG HO CHA, VICE CHAIR

- **Clinical Presentation and Neuroimaging** (Nicholas Wood / Diana Rosas / *Diane Merry* / *Kenneth Fischbeck*)
- **Polyglutamine Structure and Identification of the Toxic Species** (Paul Muchowski / Analisa Pastore / *Yvon Trottier* / *Steve Finkbeiner*)
- **Polyglutamine Disease Phenocopies and Pathogenic Mechanisms** (Russell Margolis / Tetsuo Ashizawa)
- **Cellular Pathways for Folding and Clearance of Polyglutamine Proteins** (Richard Morimoto / Ana Maria Cuervo / *Paul Taylor*)
- **Data Blitz: Focus on Novel Therapeutic Strategies** (*Beverly Davidson*)
- **Impact of Normal Function/Metabolism of Polyglutamine Proteins on Disease** (Harry Orr / Michael Hayden)
- **Cellular Sequelae in Polyglutamine Disease** (Didier Devys / Nico Dantuma / *Gillian Bates* / *Anne Messer*)
- **Dysfunction of Neuronal Circuitry** (Michael Levine / Jocelyne Caboche / *Asa Petersen*)
- **Experimental Therapeutics** (Ira Shoulson / Flint Beal / *Blair Leavitt*)
- **Keynote Address** (Christopher Ross / Jang-Ho Cha)

CANCER GENETICS & EPIGENETICS
IL CIOCCO
LUCCA (BARGA), ITALY
MAY 20-25, 2007
THOMAS JENUWEIN & EN LI, CO-CHAIRS
JEAN PIERRE ISSA, VICE CHAIR

- **Genetics vs. Epigenetics** (*Steve Baylin* / Jacqueline Lees / Andy Feinberg / Wolf Reik)
- **Chromatin Modifications and Transcription Regulation** (*Danny Reinberg* / *Shelley Berger* / Yang Shi / Sharon Dent / Robert Eisenman)
- **DNA Methylation in Cancer** (*Peter Jones* / *Adrian Bird* / Benjamin Tycko / Kathrin Muegge / Manel Esteller / Thea Tlsty / Tony Kouzarides)
- **Aneuploidy and Genome Instability** (*Maria Blasco* / *Fred Alt* / Tom Misteli / Peter Verrijzer / Ralph Scully / Maria Jasin)
- **Cancer Stem Cells** (*Maarten van Lohuizen* / Bradley Bernstein)
- **Mouse Tumor Models** (*Kristian Helin* / *Hong Wu* / Laurie Jackson-Grusby / Chuxia Deng / Clemens Schmitt / Andrew Kung)
- **Clinical Studies** (*Bob Brown* / Ramin Shiekhattar / Jean-Pierre Issa / Art Beaudet)
- **Non-Coding RNAs** (*Thomas Gingeras* / *David Livingston* / Carlo Croce)

CARDIAC ARRHYTHMIA MECHANISMS
VENTURA BEACH MARRIOTT
VENTURA, CA
MAR 18-23, 2007
IGOR EFIMOV, CHAIR
NATALIA TRAYANOVA, VICE CHAIR

- **Imaging Arrhythmias** (*Igor Efimov* / Arkady Pertsov / Guy Salama / Yoram Rudy)
- **Atrial Arrhythmias** (*Jose Jalife* / Craig Henriquez / Barry London / Omer Berenfeld)
- **Mechanoelectric Interaction** (*Natalia Trayanova* / Peter Kohl / Max Lab / Andrew McCulloch)
- **Ventricular Fibrillation** (*Robert Gilmour* / Peng-Sheng Chen / Peter Taggart / Raymond Ideker)
- **Mechanisms of Electrotherapy** (*John Wikswo* / Vladimir Fast / Blanca Rodriguez / Leslie Tung)
- **Tissue Engineering & Arrhythmia** (*Stephan Rohr* / Thomas Eschenhagen / Kit Parker / Michael Rosen)
- **Cell-Cell Communications** (*Mario Delmar* / Feliksas Bukauskas / Roselle Abraham / Eric Beyer)
- **Conduction System** (*Andre Kleber* / Greg Morley / Vadim Fedorov / Robert Gourdie)
- **Pathophysiologic Substrates of Arrhythmia** (*Douglas P. Zipes* / David Rosenbaum / Miguel Vulderabano / Tom Hund)

CAROTENOIDS
VENTURA BEACH MARRIOTT
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JAN 7-12, 2007
JOHN LANDRUM, CHAIR
SUSAN MAYNE, VICE CHAIR

- **A 3-Dimensional Basis for Chemistry and Biochemistry** (*Hans-Georg Ernst* / Madeleine Helliwell)
- **Analysis, Chemistry and Properties** (*Synnøve Liaaen Jensen* / Richard van Breemen / Klaus Albert / C. Caris-Veyrat / Harry Klee / *George Truscott*)
- **Electronic States, Photochemistry, and Photosynthesis** (*Ana Moore* / Tomas Polivka / Hideki Hashimoto / Bruno Robert / *Richard Cogdell*)
- **Human Health I: Metabolites, Gene Regulation, and Cancer** (*Helmut Sies* / X.-D. Wang / Olaf Sommerburg / John Erdman, Jr. / *Adrian Wyss*)
- **Human Health II: Nutrition & Bioavailability, an International Perspective** (*Rob Russell* / Keith West / Richard Semba / Guangwen Tang / *Machteld van Lieshout*)
- **Human Health III: Carotenoids in the Eye** (*Erik van Kuijk* / Julie Mares / Malgorzata Rozanowska / Paul Bernstein / Emily Chew / *Wolfgang Schalch*)
- **Human Health IV: Metabolites, Gene Regulation, and Cancer** (*Yoav Sharoni* / Peter Gann / Margaret Wright / Joseph Levy)
- **Carotenoids in Nature: Biosynthesis and Occurrence in Animals** (*Jonathan Blount* / Claudia Schmidt-Dannert / Eleanore Wurtzel / Kevin McGraw / Kozo Tsuchida)
- **Keynote Lecture: Carotenoid Oxidases** (*George Britton* / Johannes von Lintig)

CARTILAGE BIOLOGY & PATHOLOGY
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MAR 4-9, 2007
HENRY KRONENBERG &
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- **Pattern Control in Skeletal Development** (*Andy McMahon* / Cliff Tabin / Denis Duboule / Olivier Pourquié)
- **Signal Crosstalk in Cartilage Differentiation and Endochondral Ossification** (*Karen Lyons* / Celine Colnot / Motomi Enomoto-Iwamoto / Regis O'Keefe)
- **Control of Chondrocyte Functions** (*Mary Goldring* / Marie Demay / Reinhard Faessler / Wim van den Berg)
- **The Chondrocyte and its Extracellular Matrix: Targets in Degenerative Joint Diseases** (*Linda Sandell* / Dick Heinegard / Manuel Koch / R. Terkeltraub)
- **Cartilage Repair, Tissue Engineering, and Biomechanical Properties of Cartilage** (*Rocky Tuan* / Farshid Guilak / Ernst Hunziker)

- **Cartilage Gene Defects in Skeletal Dysplasias and Degenerative Joint Diseases**
(*William Cole* / Kathy Cheah / Stefan Mundlos / John Loughlin / Michael Briggs)
- **SOX Genes Overview**
(*Stephen Krane* / Benoit de Crombrugghe)
- **Recent Developments in Cartilage Research**
(*Bjorn Olsen* /
presentations selected from abstracts)
- **Cartilage Meets Bone**
(*William Horton* / Erwin Wagner / Gerard Karsenty)

CELL BIOLOGY OF MEGAKARYOCYTES & PLATELETS
CROWNE PLAZA
VENTURA, CA
MAR 4-9, 2007
KENNETH KAUSHANSKY, CHAIR
LESLIE PARISE &
GILBERT WHITE, CO-VICE CHAIRS

- **Gene Regulation in Megakaryocytes, Their Precursors and Progeny**
(Michele Souyri / Mortimer Poncz / Ramiro Garzon)
- **Megakaryocyte Differentiation and Platelet Biogenesis**
(*Fern Tablin* / Amy Geddis / Joe Italiano / Bill Gahl)
- **Congenital Increased and Decreased Platelet Formation and Function**
(*Alan Nurden* / Gary Gilliland / Alessandra Balduini / Warren Alexander / Kathleen Freson)
- **Inside-Out Activation of Integrins in Megakaryocytes and Platelets**
(*Mark Ginsberg* / Leslie Parise / Brian Petrich / Joel Bennett)
- **Outside-In Activation of Megakaryocytes and Platelets**
(*Sanford Shattil* / Michael Berndt / Barry Coller / Steve Watson / Mike Tomlinson)
- **Platelet Signal Transduction**
(*Lawrence Brass* / Deborah Newman / Owen McCarty / Xiaping Du)
- **Platelets and Vascular Pathophysiology**
(*Gil White* / Mary Zutter / Cristell Van Geet / Susan Smyth)
- **Megakaryocytes, Platelets and Cancer**
(*Bruce Furie* / Ajit Varki / Jay Degen / Shahin Rafii / Shaun Coughlin)
- **The Myeloproliferative Disorders**
(William Vainchenker / Radek Skoda / Stuart Orkin)

CELL CONTACT & ADHESION
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MAY 27-JUN 1, 2007
ELISABETTA DEJANA, CHAIR
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- **Basic Concepts in Adhesion and Signalling**
(*Elisabetta Dejana* / Hans Clevers / Pier Paolo Di Fiore)
- **Biology of Cadherin-Catenin Complex**
(Masatoshi Takeichi / Barry Gumbiner / G. Grunwald / Alpha Yap)
- **Control of Cell-Cell Junction Organization**
(Martin A. Schwartz / Jan L. Bos / Jennifer Stow / Andrew P. Kowalczyk)
- **Signalling Through Catenins I**
(Pierre McCrea / Walter Birchmeier / Avri Ben-Ze'ev / Katherin A. Jones)
- **Signalling Through Catenins II**
(Riccardo Fodde / Albert B. Reynolds / Fiona Watt)
- **Cell-Cell Junctions in Development**
(Rolf Kemler / Louis Reichardt)
- **Intercellular Junctions, Catenins and Cancer**
(Margaret J.Wheelock / P. Cowin / Valery Vasioukin)
- **Tight Junctions and Other Junctional Structures I**
(Ian G Macara / Maria Balda / Yoshimi Takai)
- **Tight Junctions and Other Junctional Structures II**
(Andrea McClatchey / Gherard Christofori / Dietmar Vestweber)

CHEMICAL & BIOLOGICAL TERRORISM DEFENSE
FOUR POINTS SHERATON: HARBORTOWN
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JAN 14-19, 2007
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- **The NIH Research Roadmap for Biodefense**
(*Mike Kurilla*)
- **Pathogenesis of Bacterial Diseases**
(*Emilio Garcia* / Patrick Chain / Denise Monack / Tom Kozel)
- **Pathogenesis of Viral Diseases**
(*Mike Buchmeier* / Grant McFadden / Benhur Lee / Connie Schmaljohn)
- **Biodefense Countermeasures**
(*Peter Jahrling* / Dennis Hruby / Lisa Hensley / Peter Jahrling)
- **Microarrays - Past, Present, and Future**
(*Paul Hoeprich, Jr.* / Dan Dearling / Gordon Holt / Tom Alberts)
- **Biosurveillance Through Nanoscience-Inspired Devices**
(*Jeffrey Tok* / Chad Mirkin / Hedi Mattoussi / Joseph Wang / Nicholas Fischer)
- **BioPortal Foot and Mouth Disease Project**
(*Jim Kvach* / Mark Thurmond / Hsinchun Chen / Marty Vanier)
- **Clostridia from Genome to Treatment**
(*Paul Jackson* / Karen Hill / Jim Marks / John Barr)
- **Microbial Background and Sampling**
(*Cheryl Kuske* / Allen Northrup / Charles Haas / Cheryl Kuske)

CHEMICAL REACTIONS AT SURFACES
CROWNE PLAZA
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FEB 11-16, 2007
CYNTHIA FRIEND, CHAIR
STACEY BENT, VICE CHAIR

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(*Cynthia Friend* / Sir David King / Patricia Thiel)
- **Surface Chemistry Important in Biotechnology**
(*Jennifer Hovis* / Tomoji Kawai / Joachim Spatz / Milan Mrksich)
- **Organic Functionalization of Semiconductors**
(*Julia Hsu* / Greg Lopinski)
- **Photochemical Reactions at Surfaces**
(*Michael Henderson* / Nathan Lewis / Anabella Selloni / Wilson Ho)
- **Surface Reactions in Environmental Chemistry**
(*Vicki Grassian* / Barbara Finlayson-Pitts / Jeffrey T. Roberts)
- **Imaging and Nanoscience**
(*Ulrike Diebold* / Karina Morgenstern / Bjork Hammer / Peter Sutter)
- **Functionalization of Surfaces for Biology**
(Bengt Kasemo)
- **Surface Reactions for Making Electronic Devices**
(*Melissa Hines* / Maki Kawai / Andrew Teyplyakov / Giulia Galli)
- **Surface Reactions In Catalysis**
(*Alex Harris* / Charles T. Campbell / Robert Schloegl)

CHRONOBIOLOGY
CENTRE PAUL LANGEVIN
AUSSOIS, FRANCE
MAY 6-11, 2007
TILL ROENNEBERG, CHAIR
JOSEPH TAKAHASHI, VICE CHAIR

- **Clock Watchers**
(*Anna Wirz-Justice* / Kurt Kräuchi / Frank Wilhelm)
- **Pacemaker and Input**
(*Rae Silver* / Martha Gilette / Joke Meijer / Mick Hastings / Russell Foster / *J. Woodland Hastings*)
- **Clock Genetics**
(*Martha Merrow* / Ralph Greenspan / Joseph Takahashi / Louis Ptacek)
- **Clocks in Real Life**
(*Mary Carskadon* / Charmane Eastman / Rudolfo Costa / Serge Daan / Chiara Cirelli / *Nicholas Mrosovsky*)
- **Molecular Clocks - Beyond Transcription**
(*Vijay Sharma* / Takao Kondo / Ferenc Nagy / Michael Young)
- **Multi-Oscillator Clocks**
(*Charalambos Kyriacou* / Francois Rouyer / Charlotte Förster / Urs Albrecht / Andrew Millar / *Jörg Stehle*)
- **Molecular Clocks - Increasing Complexity**
(*Jay Dunlap* / Carla Green / Carl Johnson / Michael Brunner)
- **Tissue Clocks - Slaves or Partners?**
(*Michael Menaker* / Beth Klerman / Menno Gerkema / Sato Honma / Achim Kramer / *Horiko Ueda*)
- **Blind Spots and Visions**
(*Marty Zatz* / Ueli Schibler / Martin Ralf / Sir Brian Follet)

CILIA, MUCUS & MUCOCILIARY INTERACTIONS
VENTURA BEACH MARRIOTT
VENTURA, CA
FEB 4-9, 2007
KENNETH ADLER & REEN WU, CO-CHAIRS
WIN SALE &
GEORGE WITMAN, CO-VICE CHAIRS

- **Generation and Control of Ciliary Movement**
(*Mary Porter* / *Pinfen Yang* / David Mitchell / Steven King / Elizabeth Smith)
- **Basal Bodies, Cilia Assembly and Intraflagellar Transport**
(*Lynne Quarmby* / Susan Dutcher / Douglas Cole / Nedra Wilson)
- **Primary Ciliary Dyskinesia (PCD) and Diseases of the Cilium**
(*Serge Amselem* / *Michael Leroux* / Heymutt Omran / Friedhelm Hildebrandt / Nobutaka Hirokawa)

- **Mucins and Mucus: Gene and Epigenetic Regulation**
  (*Judith Voynow* / *Sandra Gendler* / Dallas Swallow / Yin Chen / Peter Koo / Artem Loukoianov)
- **Mucins and Mucus: Disease**
  (*Scott Randell* / *Kenneth Adler* / Mary Rose / Olivera Finn / Kermit Carraway)
- **Mucins and Mucus: Development and Secretion**
  (*Burton Dickey* / *John Sheehan* / Michael Holtzman / Christopher Evans / David Erle / Duncan Rogers)
- **Mucins and Mucus: Intracellular Signaling**
  (*Reen Wu* / *C. William Davis* / Bernard Fischer / Kwang Kim / Anurag Agrawal)
- **Modeling of the System and its Components**
  (*Michael Sleigh* / *Richard Superfine* / Jonathan Howard / John Sheehan / Michael Rubenstein)
- **Airway Surface Liquid and Periciliary Fluid**
  (*Ric Boucher* / *Marcus Mall* / Robert Tarren / George Caughey / Jeffrey Wine / Steven Ballard)

DENDRITES:
MOLECULES, STRUCTURE & FUNCTION
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
MAR 18-23, 2007
MICHAEL HAUSSER &
NELSON SPRUSTON, CO-CHAIRS
ANIRVAN GHOSH &
GREGORY STUART, CO-VICE CHAIRS

- **Molecular Determinants of Dendritic Shape**
  (*Linda Van Aelst* / Liqun Luo / Franck Polleux / Yuh Nung Jan)
- **Protein Synthesis and Molecular Trafficking in Dendrites**
  (*Zoltan Nusser* / Jim Eberwine / Oswald Steward / Erin Schuman / James Trimmer)
- **Structural Plasticity of Dendrites**
  (*Kristen Harris* / Holly Cline / Elly Nedivi / Wenbiao Gan / Catherine Woolley)
- **Signal Integration in Dendrites**
  (*Rodolfo Llinas* / Jeff Magee / Matthew Larkum / Fritjof Helmchen / Jackie Schiller)
- **Computational Properties of Dendrites**
  (*Axel Borst* / Idan Segev / Arnd Roth / Bartlett Mel)
- **Dendrites and Synaptic Plasticity**
  (*Julian Jack* / Tobias Bonhoeffer / Jesper Sjöström / Arthur Konnerth)
- **Intrinsic Plasticity of Dendrites**
  (*David Linden* / Dan Johnston / Mu-ming Poo / Dominique Debanne)
- **Dendrites and Disease**
  (*Dick Tsien* / John Morrison / Terry Robinson / Brad Hyman / Bill Greenough)
- **Dendrites as Presynaptic Elements**
  (*Roger Nicoll* / Nathan Urban / Brad Alger / Wade Regehr)

GRADUATE RESEARCH SEMINAR:
DENDRITES
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
MAR 17-18, 2007
MICHAEL HAUSSER, STEFAN REMY &
NELSON SPRUSTON, CO-CHAIRS

The **Gordon-Kenan Graduate Research Seminar on Dendrites** is a two-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Dendrites: Molecules, Structure & Function** Gordon Research Conference will take place at the same location, immediately following the Seminar.

ELECTROCHEMISTRY
CROWNE PLAZA
VENTURA, CA
JAN 14-19, 2007
CAROL KORZENIEWSKI, CHAIR
VIOLA BIRSS, VICE CHAIR

- **New Sensing Strategies**
  (*Rosina Georgiadis* / Robert Hamers / Kevin Plaxco)
- **Electron and Proton Transfer**
  (*Stephen Creager* / Dennis Evans / Sharon Hammes-Schiffer / Greg Voth)
- **Electrocatalysis and Fuel Cells**
  (*Andrzej Wieckowski* / Nenad Markovic / Rohit Makharia)
- **Inorganic Materials Synthesis, Characterization and Application**
  (*Jason Ritchie* / Peter Bruce / Judith Yang / Yet-Ming Chiang)
- **Bioelectrocatalysts, Nanoparticles and Nanostructures**
  (*Carol Korzeniewski* / Andrea Russell / Shelley Minteer / Frank Zamborini)
- **Interfaces**
  (*Curtis Shannon* / Richard Van Duyne / Mark Schlossman / Victor Climent)
- **Scanning Probe Methods and Materials for Sensing**
  (*Henry White* / John Marohn / Larry Bottomley / Philippe Buhlmann)
- **Miniaturization**
  (*Carl Koval* / Ingrid Fritsch / Adam Heller)

FIBRONECTIN, INTEGRINS & RELATED MOLECULES
IL CIOCCO
LUCCA (BARGA), ITALY
APR 22-27, 2007
DEAN SHEPPARD, CHAIR
FIONA WATT, VICE CHAIR

- **Adhesive Signaling in the Vasculature**
  (Martin Schwartz / Elisabetta Dejana / Judy Varner)
- **Integrins and Inflammation**
  (Facundo Battista / Eric Brown / Yoji Shimizu / Tim Springer)
- **Cell-Matrix Interactions in 3 Dimensions**
  (Valerie Weaver / Ken Yamada / Charles Streuli)
- **Integrin Signaling**
  (Sandy Shattil / Hal Chapman / Felippo Giancotti / Mary Beckerle)
- **Integrin Activation**
  (Johannes Bos / Mark Ginsberg / David Critchley)
- **Fibronectin, Integrins and Related Molecules *In Vivo***
  (Reinhard Faessler / Fiona Watt / Louis Reichardt / Richard Hynes)
- **Cell Migration in Dictyostelium**
  (Peter Devreotes)
- **Recent Breakthroughs in Fibronectin, Integrins and Related Molecules**
  (Johanna Ivaska / Chris Turner / Alicia Arroyo)
- **Cell Migration**
  (Anna Huttenlocher / Rick Horwitz / Gregg Gundersen)

GASEOUS IONS:
STRUCTURES, ENERGETICS & REACTIONS
VENTURA BEACH MARRIOTT
VENTURA, CA
FEB 25-MAR 2, 2007
VICKI WYSOCKI, CHAIR
ALBERT VIGGIANO, VICE CHAIR

- **Photoionization and Photo Electron Imaging**
  (*Cheuk Ng* / Andrei Sanov / Ivan Powis)
- **Ion-Ion and Ion-Electron Interactions in the Gas Phase**
  (*Joshua Coon* / Scott McLuckey / Kristina (Kicki) Hakansson / Brian Mitchell)
- **Ion Surface Chemistry**
  (*Dave Russell* / Frank Turecek / Julia Laskin)
- **Theory**
  (William Hase / Susan Sinnott / Sharon Hammes-Schiffer)
- **Astrochemistry**
  (*Jurgen Troe* / Simon Petrie / Eric Herbst)
- **Ion Solvation and Hydration**
  (*Samy El-Shall* / Mark Johnson / James Lisy / Anne McCoy)
- **Gas Phase Reactions of Organic, Biological and Organometallic Species**
  (*Paul Wenthold* / Balint Sztaray / Jeehiun K. Lee)
- **Spectroscopy of Ions**
  (*Rebecca Jockush* / Robert Dunbar / Thomas Rizzo / Joel Parks)
- **Ion Mobility (Featured Speaker)**
  (Michael Bowers)

GLIAL BIOLOGY: FUNCTIONAL INTERACTIONS AMONG GLIA & NEURONS
CROWNE PLAZA
VENTURA, CA
MAR 11-16, 2007
VLADIMIR PARPURA, CHAIR
BRUCE RANSOM, VICE CHAIR

- **Effects of Growth Factors on Glial Growth, Differentiation and Function**
  (*Tika Benveniste* / Wilma Friedman / Cheryl Dreyfus / Freda Miller / Robert Malenka)
- **Interactions of Signaling and Metabolic Molecules**
  (*Gerald Dienel* / Arne Schousboe / Sebastián Cerdán / Juan Bolaños / Bruce Ransom)
- **Control of Vasculcature by Glial Cells**
  (*Bruce Ransom* / Maiken Nedergaard / Giorgio Carmignoto / Eric Newman / Brian MacVicar)
- **Molecular Dissection of Microglial Interactions with Neurons and Glia**
  (*Jane Relton* / Monica Carson / Richard Ransohoff / Richard Banati / Wen-Biao Gan)
- **Astrocyte and NG2$^+$ Cell Heterogeneity nn the Mammalian CNS**
  (*Harold Kimelberg* / Min Zhou / Dwight Bergles / Christian Steinhauser / Michael Brenner / Tailoi Chan-Ling)
- **Gap Junctions in Astrocytic Physiology and Pathology**
  (*David Spray* / Tammy L. Kielian / Zu-Cheng Ye / Christian Naus / Christian Giaume)

- **Water, Calcium and Ligand Dynamics in Glia**
  (*Ken McCarthy* / Joachim Deitmer / Helmut Kettenmann / Ole Petter Ottersen / Sergio Ojeda / Shumin Duan)
- **Glia Listening and Talking to Synapse**
  (*Douglas Fields* / Alfonso Araque / Gary Westbrook / Richard Robitaille / Philip Haydon)
- **Glia in Neuropathology**
  (*Philip Haydon* / Serge Rivest / Kazuhide Inoue / Luc Vallieres / Harald Sontheimer / James Lechleiter)

GLYCOBIOLOGY
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
MAR 4-9, 2007
KAREN COLLEY, CHAIR
CHRISTOPHER WEST, VICE CHAIR

- **Evolutionary and Developmental Glycobiology**
  (*Pamela Stanley* / Ajit Varki / Yu Yamaguchi / Jan Hofsteenge)
- **Cancer Glycobiology**
  (*Michael Pierce* / Jim Dennis / Pauline Rudd / Jeff Esko)
- **Glycobiology of Microbes and Parasites**
  (*Anant Menon* / Malcolm McConville / Susan Logan / Noorjahan Panjwani)
- **Biosynthesis of Glycoconjugates**
  (*Carlos Hirschberg* / *Phil Robbins* / Ariel Orellana / Debra Mohnen / Paul Weigel / Jacques Baenziger)
- **Quality Control in Glycoconjugate Biosynthesis**
  (*William Lennarz* / Robert Haltiwanger / Minoru Fukuda / Richard Cummings)
- **Glycomics and Structure**
  (*Anne Dell* / Minoru Harehisa / Lara Mahal / Kelley Moremen / Tim Fritz)
- **Glycoimmunology**
  (*James Paulson* / Paul Crocker / Hermann Ziltener / Linda Baum)
- **Glyconeurobiology**
  (*Michael Tiemeyer* / David Van Vactor / Huaiyu Hu / Ron Schnaar / Chihiro Sato)
- **Glycobiology of Disease**
  (*Gerald Hart* / Michael Demetriou / Lance Wells / Jeffrey Ravetch)

GRADIENT SENSING & DIRECTED CELL MIGRATION
CROWNE PLAZA
VENTURA, CA
JAN 28-FEB 2, 2007
JEFFREY SEGALL, CHAIR
ANNA HUTTENLOCHER, VICE CHAIR

- **Gradient Sensing and Modeling Overviews**
  (Peter Devreotes / Douglas Lauffenburger)
- **Directed Migration Systems 1**
  (Yi Rao / Pernille Rorth / Erez Raz)
- **Directed Migration Systems 2**
  (John Condeelis / Judith Van Houten / Richard Lewis)
- **Receptor Signaling**
  (Nancy Hynes / Ann Richmond / Patrick Mehlen / Boris Kholodenko)
- **PI3 Kinase Roles in Migrating Cells**
  (Dianqing Wu / Christian Rommel / Jason Haugh / Pablo Iglesias)
- **Small G Protein Functions in Migrating Cells**
  (Alan Hall / Paul Martin / Peter Pryciak / Britta Eickholt)
- **Downstream Signaling Pathways**
  (Richard Firtel / Moo-ming Poo / Tobias Meyer)
- **Signaling to the Cytoskeleton 1**
  (Ann Ridley / Orion Weiner / Gary Bokoch)
- **Signaling to the Cytoskeleton 2**
  (Gregg Gundersen / Scott Simon / David Soll)

GRADUATE RESEARCH SEMINAR: BIOINORGANIC CHEMISTRY
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
FEB 1-4, 2007
TROY STICH, CHAIR
SAMUEL PAZICNI, VICE CHAIR

- **Bio-Inspired/Applied Bioinorganic Chemistry**
  (*Sonya Franklin* / Jen Wong / Matt Kieber-Emmons / Richard M. Watson)
- **Cofactor Biosynthesis/Incorporation**
  (*Dennis Dean* / Larry Vickery Student / Robert Burnap Student)
- **Metalloenzyme Structure Determination**
  (*Tim Machonkin* / Yulia Pushkar / Abishek Dey)
- **Computational Insights into Metalloenzyme Electronic Structure**
  (*Thomas Brunold* / Michael Newcomer / Frank Neese Student)
- **Metalloenzyme Mechanism and Function**
  (Dominique Padovani / Michael Marletta Student)

HYDROCARBON RESOURCES
CROWNE PLAZA
VENTURA, CA
JAN 7-12, 2007
KOICHI MIURA, CHAIR
PHILLIP BRITT, VICE CHAIR

- **Computational Chemistry**
  (*Phil Britt* / Matthew Neurock)
- **Catalysts for Various Hydrocarbons**
  (*Kathleen Carrado* / Bruce R. Cook / Robert Davis / Johannes A. Lercher / Roel Prins)
- **Advanced Analytical Techniques**
  (*Randy Winans* / Peter Chupas / Bert M. Weckhuysen)
- **Novel Carbon Materials**
  (*Hank Foley* / *Hiroaki Hatori* / Takashi Kyotani / Diego Cazorla / Pulickel A. Ajayan)
- **Heavy Oil**
  (*Ikuo Saito* / *Phillip Smith* / Murray Gray / Ryuzo Tanaka)
- **Hydrogen / Production and Storage**
  (*Tom Autrey* / *Nobuhiro Kuriyama* / Guido P. Pez / Osamu Okada / Randy Cortright)
- **Hydrogen / Fuel Cell**
  (*Tom Autrey* / *Dave King* / Scott Barnet / Zenpachi Ogumi)
- **Combustion and Gasification with CO_2 Sequestration**
  (*Ron Pugmire* / *Hisao Makino* / Yuichi Fujioka)
- **Distinguished Speaker Session**
  (*Kouichi Miura* / George A. Olah)

IMMUNOCHEMISTRY & IMMUNOBIOLOGY
VENTURA BEACH MARRIOTT
VENTURA, CA
MAR 25-30, 2007
FIONA POWRIE, CHAIR
MITCHELL KRONENBERG, VICE CHAIR

- **Development of the Immune System**
  (*Hergen Spits* / Katia Georgopoulos / Albert Bendelac / Hans-Reimer Rodewald)
- **Evolution of Self-Non-Self Recognition Strategies in the Immune System**
  (*Mitchell Kronenberg* / Deitmar Schmucker / Tom Boehm / Max Cooper / Tony De Tomaso)
- **Innate Immunity**
  (*Ruslan Medzhitov* / Akiko Iwasaki / Richard Locksley / Caetano Reis e Sousa)
- **Antigen Presentation and Lymphocyte Activation**
  (*Gary Koretzky* / Nilabh Shastri / Peter Cresswell / Susan Pierce)
- **Dynamics of Leukocyte Interactions**
  (*Uli von Andrian* / Mark Davis / Ronald Germain / Avi Kupfer)
- **TNF and Ig Family Costimulatory Pathways**
  (*Arlene Sharpe* / Michael Croft / Jim Allison / Simon Davis)
- **Tolerance and Autoimmunity**
  (*Alexander Rudensky* / Dan Cua / Diane Mathis / Richard Flavell)
- **Mucosal Immunity**
  (*Adrian Hayday* / Andrew Macpherson / Dana Philpott / Hans-Christian Reinecker)
- **Infectious Disease**
  (*Rafi Ahmed* / Christine Biron / Stephan Kaufman / Yasmine Belkaid)

INORGANIC REACTION MECHANISMS
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
FEB 18-23, 2007
ANDREJA BAKAC, CHAIR
CLARK LANDIS, VICE CHAIR

- **Metal-Mediated Oxidations**
  (*Jack Norton* / Jim Mayer / Steve Lippard)
- **Oxygen Activation and Electron Transfer**
  (*David Stanbury* / Justine Roth / Mahdi Abu Omar / Bill Gong / Shunichi Fukuzumi)
- **Iron**
  (*Rudi van Eldik* / Jonas Peters / Wonwoo Nam)
- **Hydrogen and Carbon Monoxide**
  (*Ayusman Sen* / Marcetta Darensbourg / Brian James / Tom Baker / Dan DuBois)
- **Bioinorganic**
  (*Al Crumbliss* / Jeremy Harvey / Lisa Berreau)
- **Organometallics**
  (*Clark Landis* / Susannah Scott / Kevin Shaughnessy / Melanie Sanford / Malcolm Chisholm)
- **Nitrogen and Phosphorus**
  (*Shannon Stahl* / Paul Chirik / Chris Cummins)
- **Polyoxometalates and Other Clusters**
  (*Ronny Neumann* / Craig Hill / William Casey / Richard Finke)
- **Special Lecture: Solar Photochemistry**
  (*Dale Margerum* / Harry Gray)

INSULIN-LIKE GROWTH FACTORS IN PHYSIOLOGY & DISEASE
CROWNE PLAZA
VENTURA, CA
MAR 18-23, 2007
CHERYL CONOVER, CHAIR
PETER ROTWEIN, VICE CHAIR

- **IGFs: Back to the Future**
  (*Cheryl Conover* / Robert Baxter / James Kirkland)
- **Physiology**
  (*Terri Wood* / Ross Clark / Kim Heidenreich)
- **Structure/Function**
  (*Jeff Holly* / Pierre DeMeyts / Claus Oxvig)
- **Intracellular Signaling**
  (*Eva Feldman* / George Thomas / Rosemary O'Connor)
- **IGF Binding Proteins**
  (*Zee Upton* / Cliff Rosen / Gordon Allan)
- **Diabetes, Metabolism, Obesity**
  (*Robert Smith* / David Clemmons / Charles Roberts)
- **Cancer**
  (*Doug Yee* / Lee Helman / Adrian Lee)
- **Development & Aging**
  (*Cunming Duan* / Victor Han / Marc Tatar)
- **Newly Emerging Topics**
  (*Derek Leroith* / Ignacio Torres Aleman / Anna Spagnoli)

MAMMALIAN DNA REPAIR
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
FEB 4-9, 2007
PRISCILLA COOPER, CHAIR
ALAN D'ANDREA, VICE CHAIR

- **Keynote Talk 1: Genome Maintenance Through Recombination**
  (Roland Kanaar)
- **Keynote Talk 2: How Telomeres Deal with DNA Repair Pathways**
  (Titia de Lange)
- **Coordination of Excision Repair / Pathway Intersections**
  (*Alan Tomkinson* / Wim Vermeulen / Jean-Marc Egly / Sankar Mitra)
- **Repair of Endogenous DNA Damage**
  (*Samuel Wilson* / Margherita Bignami / Akira Yasui / Joann Sweasy)
- **DNA Repair and Transcription**
  (*Philip Hanawalt* / Kiyoji Tanaka / Leon Mullenders / Gijsbertus van der Horst / Bernd Epe)
- **Chromatin Structure and DNA Repair**
  (*Michael J. Smerdon* / Mary Ann Osley / Genevieve Almouzni)
- **DNA Damage Responses and Managing Genomic Stability**
  (*Alan D'Andrea* / Gerard Evan / Leona Samson / Michael Yaffe / David Toczyski)
- **Mismatch Repair**
  (*Paul Modrich* / Peggy Hsieh / Lorena Beese)
- **Double-Strand Break Repair and Genomic Stability**
  (*Steve Jackson* / Simon Powell / Eric C. Greene / John Tainer / Penny Jeggo)
- **Polymerase Management / Replication of Damaged DNA**
  (*Alan Lehmann* / Thomas Kunkel / Graham Walker / John Wittschieben)

METALS IN BIOLOGY
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
JAN 28-FEB 2, 2007
ROBERT SCOTT, CHAIR
JULIE KOVACS, VICE CHAIR

- **Metalloprotein Crystal Structures**
  (*David M. Dooley* / Hans C. Freeman)
- **Nonheme Iron**
  (*Julie Kovacs* / J. Martin Bollinger / Andrew S. Borovik / John D. Lipscomb / Donald M. Kurtz, Jr.)
- **NO Chemistry and Biology**
  (*Judith Burstyn* / Bruce Demple / Brian R. Crane / Nicholas J. Watmough)
- **Metal-Radical Chemistry**
  (Ruma Banerjee / Wolfgang Buckel / Kurt Warncke / Squire J. Booker)
- **Metalloprotein Design & Engineering**
  (Shigeru Negi / Brian R. Gibney / Michael Y. Ogawa)
- **Photosystem II Oxygen-Evolving Complex**
  (*David Britt* / Jan Kern / Vittal K. Yachandra / Wolfgang Lubitz / Gary W. Brudvig)
- **Applications of Time-Resolved Techniques**
  (*Jim Penner-Hahn* / Brian Bennett / R. Brian Dyer / Holger Dau)
- **Metal Homeostasis**
  (*Dennis Winge* / Valeria Culotta / Lucia Banci / Sabeeha Merchant / Marc Solioz)
- **Joint Session with Graduate Research Seminar on Bioinorganic Chemistry**
  (*Robert A. Scott* / Christopher T. Walsh)

MOLECULAR PHARMACOLOGY
VENTURA BEACH MARRIOTT
VENTURA, CA
JAN 28-FEB 2, 2007
MARK VON ZASTROW, CHAIR
JOEL BOCKAERT &
SUSANNA COTECCHIA, CO-VICE CHAIRS

- **Structure**
  (*Kris Palczewski* / Dan Muller / John Tesmer / Gebhart Schertler)
- **Molecular Dynamics**
  (*Brian Kobilka* / Roger Sunahara / Dave Farrens / Martin Lohse)
- **Signaling Networks**
  (*Steve Sprang* / John Scott / Michel Bouvier / Steve Lanier)
- **Regulation and Membrane Traffic**
  (*Sudha Shenoy* / Jeff Benovic / JoAnn Trejo / Henrik Dohlman)
- **Ligand Diversity**
  (*Joel Bockaert* / Jerold Chun / Bryan Roth / Taroh Iiri)
- **Effector Systems**
  (*Diane Barber* / David Julius / Silvio Gutkind / Orion Weiner)
- **CV Pharmacology and Development**
  (*Susanna Cotecchia* / Shaun Coughlin / Ulrike Gaul)
- **Neuropharmacology and Behavior**
  (*Marc Caron* / Francis Lee / Nigel Bunnett / Jennifer Whistler)
- **Emerging Opportunities**
  (*Lee Limbird* / Paul Insel / Olivier Civelli / Joan Heller Brown)

MYOGENESIS
IL CIOCCO
LUCCA (BARGA), ITALY
MAY 13-18, 2007
STEPHEN TAPSCOTT, CHAIR
NADIA ROSENTHAL, VICE CHAIR

- **Comparative Biology**
  (Scott Gilbert / Eric Olson / Mark Martindale)
- **Developmental Specification**
  (*Charles Ordahl* / Olivier Pourquie / Margaret Buckingham / Andrew Lassar / Shahragim Tajbakhsh / Gabrielle Kardon / Andrea Munsterberg / Pascal Maire)
- **Invertebrate and Vertebrate Muscle**
  (*Susan Abmayr* / Michael Krause / Katja Seipel / Rie Kusakabe / Mary Baylies)
- **Muscular Dystrophies**
  (*Kay Davies* / Maurice Swanson / Peter Currie / Elizabeth McNally / Silvere van der Maarel / Luis Garcia)
- **Transcription**
  (*Peter Rigby* / Richard Harvey / Anthony Imbalzano / Pura Munoz-Canoves / Vittorio Sartorelli)
- **Regeneration**
  (*Terry Partridge* / Michael Rudnicki / Giulio Cossu / Elly Tanaka / Tom Rando / Graciella Unguez / Elizabeth Chen)
- **Systems Biology**
  (*Barbara Wold* / Alan Michelson / Susan Mango / Brian Dynlacht / Eileen Furlong)
- **Signaling and Plasticity**
  (*Leslie Leinwand* / Nadia Rosenthal / Steve Burden / Ravi Kambadur / David Glass / Eyal Bengal / John McDermott)
- **Cancer and Growth**
  (*Stephen Tapscott* / Lorenzo Puri / David Sassoon)

NEW FRONTIERS IN CANCER DETECTION & DIAGNOSIS
CROWNE PLAZA
VENTURA, CA
JAN 21-26, 2007
DAVID SIDRANSKY, CHAIR
WILLIAM BIGBEE, VICE CHAIR

- **Biology of Early Cancer Detection I**
  (*David Sidransky* / *Sudhir Srivastava* / David Sidransky / Henry Lynch / Brian Reid)
- **Biology of Early Cancer Detection II**
  (*Thea Tlsty* / *Michael (Tony) Hollingsworth* / Thea Tlsty / Michael (Tony) Hollingsworth / Wilbur Franklin / Chris Counter / Lynn Hartman)
- **Enabling Technologies for Biomarker Discovery**
  (*Joe Gray* / *Anna Lokshin* / Jim Felton / David Ward / John Conboy)
- **Genomics-Based Diagnostic Biomarkers**
  (*Arul Chinnaiyan* / *Ann Killary* / Matthew Meyerson / Bert Vogelstein / Ken Kinzler / Linda Chin / Scott Hammond)
- **Omics as Biomarkers: Glycomics, Lipidomics, Metabolomics**
  (*Timothy Block* / *Pauline Rudd* / Eiji Miyoshi / Anand Mehta / Minora Fukuda / Margaret Hufljet)
- **State of Proteomics**
  (*Bill Bigbee* / *Karen Rodland* / Steve Carr / Raju Kucherlapati / Joshua LaBaer / Tom Conrads)
- **Epitomics and Immunomics**
  (*Samir Hanash* / *Karen Anderson* / Michael Tainsky / David Beer / William Hancock / Ian Tanner)

- **Biomarkers at a Crossroads: A Clinical Reality Check**
  (*Alan Partin* / *Laura Esserman* / Ian Thompson / Dan Hayes / Rick Klausner / Rob Lipshutz / Sean Tunis)
- **Data Mining Based Biomarker Discovery**
  (*Ken Buetow* / *Dan Crichton* / Anthony Finkelstein / Jimmy Eng / Andre Califano)

NITRIC OXIDE
CROWNE PLAZA
VENTURA, CA
FEB 4-9, 2007
WILLIAM SESSA, CHAIR
DAVID WINK, VICE CHAIR

- **Perspectives in NO Research (Keynote Lectures)**
  (*Steven Gross* / Salvador Moncada / Betty Sue Masters / Alexander Varchavsky)
- **NO Generating/Sensing Pathways: Structure and Function**
  (*Brian Crane* / Elizabeth Getzoff / William Montfort / Dennis Stuehr / C.S. Raman)
- **In Vivo Chemistry and Actions of NO: NO Adducts or cGMP Signaling**
  (*Charlie Lowenstein* / Mark Gladwin / Joan Mannick / Doris Koesling)
- **Uncoupled NOS: Is it Real In Vivo? Mechanisms and Pathophysiology**
  (*Kirk Pritchard* / Bernd Mayer / Jay Zweier / Rudi Busse)
- **Cellular Biology of NO and NOS**
  (*David Fulton* / Tim Billiar / NT Eissa / Charles Lowenstein)
- **Termination of NO Signaling**
  (*Ferid Murad* / Harry Ischiropoulos / Limin Liu / Sharron Francis)
- **Roles of NO in Physiology and Pathophysiology**
  (*Gabor Rubanyi* / Patrick Vallance / James Tidball / David Roberts / Kenneth Bloch)
- **Therapeutic Strategies Aimed at Regulating NO Biology**
  (*Louis Ignarro* / Vijay Shah / Jane Connor / Warren Zapol)

ORGANIC THIN FILMS
CENTRE PAUL LANGEVIN
AUSSOIS, FRANCE
MAY 27-JUN 1, 2007
MARTIEN COHEN STUART &
NICHOLAS KOTOV, CO-CHAIRS
DEBORAH LECKBAND &
CHAIM SUKENIK, CO-VICE CHAIRS

- **Smart Capsules I**
  (*Matthew Tirrell* / Gleb Sukhorukov / Wolfgang Maier)
- **Smart Capsules II**
  (*Matthew Tirrell* / Marcel Boehmer / Adi Eisenberg)
- **Mechanically Active (Bio)Surfaces I**
  (*Martien Cohen Stuart* / Svetlana Santer / Manfred Stamm)
- **Mechanically Active (Bio)Surfaces II**
  (*Martien Cohen Stuart* / Jasper van der Gucht)
- **Self-Assembly and Nanostructuring I**
  (*Wolgang Maier* / Ulrich Steiner / Matthew Tirrell)
- **Self-Assembly and Nanostructuring II**
  (*Wolgang Maier* / Stefan Zauscher / Georg Krausch / Frans Leermakers)
- **Biofunctional Surfaces I**
  (*Marcel Boehmer* / Juergen Ruehe / Harm-Anton Klok)
- **Biofunctional Surfaces II**
  (*Marcel Boehmer* / Paul Van Tassel / Marcus Textor / Dennis Disher)

OXIDATIVE STRESS AND DISEASE
VENTURA BEACH MARRIOTT
VENTURA, CA
MAR 11-16, 2007
C.S. RAMAN &
BENNETT VAN HOUTEN, CO-CHAIRS
KELVIN DAVIES &
HOLLY VAN REMMEN, CO-VICE CHAIRS

- **Keynote Lecture 1: Iron Homeostasis, Oxidative Stress and Human Disease**
  (Tracey Rouault)
- **Keynote Lecture 2: A Mitochondrial Paradigm of Metabolic and Degenerative Diseases, Aging and Cancer**
  (Douglas Wallace)
- **Stem Cell Survival and Oxidative Stress**
  (*Toshio Suda* / John Sedivy)
- **Neurodegeneration and Oxidative Stress**
  (*Leo Pallanck* / Ted Dawson / Julie Andersen / Jeffrey Rothstein)
- **Oxidative Stress in Lung Injury and Asthma**
  (*Steve Kleeberger* / Anne Perraud / Brooke Mossman)
- **Cancer and Oxidative Stress**
  (*Natalie Mazure* / Paul Schumacker / Yousin Suh / Jan Vigj / Virpi Launonen)
- **Diabetes and Oxidative Stress**
  (*Michael Brownlee* / Evan Rosen / Gerald Shulman / Mary Loeken)
- **Biomarkers of Oxidative Stress and Inflammation**
  (*Jason Morrow* / Ned Porter / Francisco Schopfer / Valeria Culotta / Kelvin Davies)
- **Cardiovascular Disease and Oxidative Stress**
  (*Ajay Shah* / Joshua Hare)
- **Biology of Iron and Iron Overload Disorders**
  (*James Imlay* / Matthias Hentze / Jill Waalen / Nicholas DiProspero)
- **Mitochondria and Oxidative Stress**
  (*Michael Murphy* / William Copeland / Roderick Capaldi / Gerald Shadel / Massimo Zeviani / Paul Hwang / Christopher Baines)
- **Aging and Oxidative Stress**
  (*Nils Goran Larsson* / Tomas Prolla / Boudewijn Burgering / Azad Bonni / Holly Van Remmen)

PLANT HERBIVORE INTERACTION
CROWNE PLAZA
VENTURA, CA
FEB 18-23, 2007
RICHARD LINDROTH, CHAIR
MARTINE RAHIER, VICE CHAIR

- **Evolutionary History and Ecological Consequences of Variation in Plant Chemical Defense**
  (Tom Mitchell-Olds)
- **Functional Genomics, Biochemistry and Physiology**
  (Jack Schultz / Peter Constabel / Colin Orians & Ben Babst / Marcel Dicke)
- **Looking Forward: The Future for Plant-Herbivore Interactions Research**
  (Ian Baldwin / May Berenbaum)
- **Multi-Species and Indirect Interactions**
  (Ted Turlings / Rebecca Irwin / Alan Gange / Urs Schaffner)
- **Plant-Herbivore Interactions in Marine Systems**
  (Gunilla Toth / Emmet Duffy)
- **Plant-Herbivore Interactions in Evolutionary Perspective**
  (Susanne Dobler / Douglas Futuyma / Phyllis Coley / Barbara Roy)
- **Plant-Herbivore Interactions and Global Change**
  (Carlos Ballare / Lesley Hughes)
- **Plant-Herbivore Interactions at Large Organizational and Spatial Scales**
  (John Bishop / Claudio Gratton / Brad Potts / Stephan Hättenschwiler)
- **Looking Back: Plant-Herbivore Interactions in Historical Perspective**
  (Conrad Labandeira / Peter Price)

POLAR MARINE SCIENCE
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
MAR 25-30, 2007
KEVIN ARRIGO, CHAIR
DAVID THOMAS, VICE CHAIR

- **All Things Great and Small: Interactions at Multiple Scales**
  (Eddy Carmack / Paul Tregeur)
- **Zooming In: Processes at the Limits of Detection 1**
  (Peter Franks / Dave Caron / Jody Deming)
- **Zooming In: Processes at the Limits of Detection 2**
  (Gerhard Herndl / Jean-Eric Tremblay)
- **Causes and Consequences of Patchiness**
  (Laurie Padman / Mark Moore / Nina Karnovsky)
- **Mesoscale Physics and Biology**
  (David Holland / Rebecca Korb)
- **Coupling at the Boundaries**
  (Christine Michel / Kelly Falkner / Ted Scambos)
- **Surface and Deep Water Interactions**
  (Robert Pickart / Lee Cooper)
- **The "Big Picture"**
  (George Hunt / Bob Dickson / Nicole Lovenduski / Cynthia Tynan)
- **Zooming Out: Taking the Longer View**
  (Daniel Sigman / Steven Emslie)

POLYMERS (WEST)
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
JAN 7-12, 2007
JIMMY MAYS, CHAIR
DARRIN POCHAN, VICE CHAIR

- **Bioactive Polymers**
  (*J. Pochan* / Greg Tew / Darrin Pochan / Grant Smith)
- **Controlled Polymer Architectures**
  (*G. Coates* / Robert Grubbs / Nikos Hadjichristidis)
- **Polymers for Microelectronics and Optics**
  (Lynn Loo / Ned Thomas / Ken Carter)
- **Block Copolymers**
  (*J. Hedrick* / Yves Gnanou / Barney Grubbs)
- **Nanoparticles and Nanotechnology**
  (*G. Liu* / Sergei Sheiko / Chris Soles / Bin Zhao)

- **Bio-Rheology and Gels**
  (*W. de Groot* / Ron Larson / Julia Kornfield / Simon Ross-Murphy)
- **Polymers for Energy Needs**
  (*David Lohse* / Rigoberto Advincula / Steven Holdcroft)
- **Polymer Films and Interfaces**
  (*Christine Landry* / Mike Kilbey / Mark Dadmun)
- **Chromatography and Microfluidics**
  (Taihyun Chang / Eugenia Kumacheva)

GRADUATE RESEARCH SEMINAR: POLYMERS (WEST)
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
JAN 5-7, 2007
JIMMY MAYS, CHAIR

The **Gordon-Kenan Graduate Research Seminar on Polymers (West)** is a two-day Gordon Conference-style meeting exclusively for graduate students and postdoctoral fellows. Speakers will be chosen from among the attendees. The **Polymers (West)** Gordon Research Conference will take place at the same location, immediately following the Seminar.

QUANTITATIVE GENETICS AND GENOMICS
VENTURA BEACH MARRIOTT
VENTURA, CA
FEB 18-23, 2007
PATRICK PHILLIPS, CHAIR
DANIEL POMP, VICE CHAIR

- **Two Decades of Quantitative Genetics and Genomics**
  (*Patrick Phillips* / Eugene Eisen)
- **Genome-wide Association Mapping**
  (Richard Mott / Magnus Nordberg)
- **Gene Expression and Mapping**
  (Leonid Krugliak / Eric Schadt)
- **Statistical Genomics**
  (Rebecca Doerge / David Allison / Manolis Dermitzakis)
- **Collaborative Crosses**
  (Ed Buckler / Elisa Chesler)
- **Selection and Mapping in Animal Models**
  (*Daniel Pomp* / Jerry Taylor / Archie Clutter)
- **Selection and Mapping in Natural Populations**
  (Hopi Hoekstra / Andy Clark)
- **Quantitative Genomics of Behavior**
  (Trudy Mackay / Charles Whitfield)
- **Quantitative Genetics and Species Differences**
  (John Willis / David Houle)
- **Variation in Developmental Systems**
  (Fred Nijhout / William Cresko)

QUANTUM INFORMATION SCIENCE
IL CIOCCO
LUCCA (BARGA), ITALY
APR 15-20, 2007
MICHEL DEVORET &
ROBERT SCHOELKOPF, CO-CHAIRS
IMMANUEL BLOCH &
DAVID DIVINCENZO, CO-VICE CHAIRS

- **New Directions in Quantum Information**
  (Isaac Chuang / Nicolas Gisin)
- **Photons and Atoms**
  (*Hideo Mabuchi* / Eugene Polzik / Paul Kwiat / Philippe Grangier)
- **Trapped Ions**
  (*Rainer Blatt* / Dietrich Leibfried / Chris Monroe)
- **Artificial Solid State Qubits**
  (*Daniel Esteve* / Yasunobu Nakamura / Leo Kouwenhoven / Amir Yacoby)
- **Microscopic Condensed Matter Qubits**
  (*David Cory* / Misha Lukin / Wolfgang Wernsdorfer)
- **Real and Artificial Atoms Coupled by Harmonic Modes**
  (Jean-Michel Raimond / Keith Schwab / Atac Imamoglu)
- **Theory of Quantum Information**
  (*Artur Ekert* / Hans Briegel / Daniel Gottesman)
- **Arrays of Atoms and Molecules Held by Photons**
  (*Peter Zoller* / Immanuel Bloch / David DeMille / Dieter Meschede)
- **Atom Chips and Hybrid Technologies**
  (*Jakob Reichel* / Jorg Schmiedmayer / Ed Hinds)

RED CELLS
CENTRE PAUL LANGEVIN
AUSSOIS, FRANCE
MAY 20-25, 2007
JON MORROW, CHAIR
JAMES BIEKER, VICE CHAIR

- **Developmental Aspects of Hematopoiesis**
  (*Len Zon* / Nancy Speck / Margaret Baron / Roger Patient / Kyunghee Choi / Elaine Dzierzak)
- **Membrane-Cytoskeletal Protein Interactions**
  (*Mohandas Narla* / Velia Fowler / Athar Chishti / Phillip Low / Graham Thomas / Kasturi Haldar)
- **Global Regulation of Gene Expression**
  (*Doug Engle* / Frank Slack / Frank Grosveld / George Stam / Peter Fraser / Doug Higgs)
- **Transcription Factors**
  (*Stuart Orkin* / Michael Bender / Emory Bresnick / John Crispino / Joyce Lloyd / Sjaak Phillipsen / Gerg Blobel)
- **Control of Protein Diversity During Erythropoiesis**
  (*Edward Benz* / David Bodine / Patrick Gallagher / John Conboy / Masi Yamamoto / Mitch Weiss)
- **Signaling in Mature and Developing Red Cells**
  (*Phillip Low* / David Williams / James Palis / Leslie Parisi / Kay Macleod / Don Wojchowski)
- **Phenotypic Transition During Erythroid Differentiation**
  (*Samuel Lux* / Harvey Lodish / Joel Chassis / Mark Koury / Mangeat Hanspal)
- **Red Cell Membrane Structure and Dynamics**
  (*Vincent Marchesi* / David Speicher / Dennis Discher / Xuli An / Athur Baines / John Gibson)
- **Red Cell Disorders**
  (*Peter Agre* / Alan D'Andrea / Robert Browdsky / Yves Colin / Luanne Peters)

RENEWABLE ENERGY: SOLAR FUELS
VENTURA BEACH MARRIOTT
VENTURA, CA
JAN 21-26, 2007
DANIEL NOCERA, CHAIR
NATHAN LEWIS, VICE CHAIR

- **Global Energy Perspective**
  (*Harry B. Gray* / Richard Somerville / Nathan S. Lewis)
- **Bioenergy Conversion: Systems**
  (P*. Leslie Dutton* / Jim Barber / Shelagh Ferguson-Miller / Juan Fontecilla-Camps / Maria Ghirardi)
- **Bioenergy Conversion: Mechanisms**
  (*Richard S. Eisenberg* / Leif Hammarström / Thomas Moore / Fraser A. Armstrong)
- **Small Molecule Activation: Oxygen, Hydrogen and Water**
  (*Christopher C. Cummins* / David Milstein / Jonas C. Peters / Daniel L. Dubois / Thomas J. Meyer)
- **Other Small Molecule Activation Reactions of Energy Consequence**
  (*John E. Bercaw* / Joseph P. Sadighi / Shannon S. Stahl / Karen I. Goldberg)
- **Hydrogen Storage**
  (*Jeffrey R. Long* / Andreas Züttel / Omar M. Yaghi / Tom Baker)
- **Reaction Chemistry at Surfaces**
  (*Allen J. Bard* / T. Don Tilley / Joseph T. Hupp / Hrvoje Petek)
- **Photovoltaics**
  (*Arthur Nozik* / Paul Alivisatos / Michael D. McGehee / Stephen R. Forrest)
- **Government and Industry Perspective**
  (*Karen J. Brewer*)

RNA EDITING
VENTURA BEACH MARRIOTT
VENTURA, CA
JAN 14-19, 2007
MARY O'CONNELL &
KENNETH STUART, CO-CHAIRS
JUAN ALFONZO &
MARIE OHMAN, CO-VICE CHAIRS

- **Diversity in Editing**
  (*Robert Reenan* / Henri Grosjean / Jonatha M. Gott / Nicholas Davidson)
- **Sno and Other Stable RNA Modifications**
  (*Eric Phizicky* / Michael W. Gray / YiTao Yu / Maurille Fournier / Axel Brennicke / Tom Meier)
- **Innate Immune Response and Host Defense**
  (*Bryan Cullen* / Reuben Harris / Nina Papavasiliou / Charles Samuel)
- **Macromolecules Machines and Functional Interactions**
  (*Barbara Sollner-Webb* / Christian Schmitz-Linneweber / Larry Simpson / Harold C. Smith / Donna Koslowsky / Juan Alfonzo / Steve Hajduk)
- **Editing and RNA Interference**
  (*Kazuko Nishikura* / Deirdre Scadden / Gordon Carmichael / Brenda Bass)
- **Enzyme-Substrate Recognition**
  (*Joshua Rosenthal* / Peter Beal / Maureen Hanson / Marie Öhman / Warner Greene / Laurie Read / Frédéric Allain)
- **Structure**
  (*Wim Hol* / Juli Feigon / Michael P. Terns / Adrian R. Ferre-D'Amare)

- **Medical Consequences**
  (*Ron Emeson* / Michael Jantsch /
  Peter Seeburg / Youming Lu / Shin Kwak /
  Nathaniel Landau / Ingo Greger)
- **Hot Topics**
  (talks chosen from submitted abstracts)

SALIVARY GLANDS & EXOCRINE SECRETION
VENTURA BEACH MARRIOTT
VENTURA, CA
FEB 11-16, 2007
DAVID ANN, CHAIR
MARY REYLAND &
DAVID YULE, CO-VICE CHAIRS

- **Opening of Meeting:**
  Genes and Salivary Development
  (*Mary Reyland* / Kenneth M. Yamada /
  Ray MacDonald)
- **Lacrimal Gland, Dry Eye, and**
  Sjogren's Syndrome
  (*Sarah Hamm-Alvarez* / *Monn Myat* /
  Darlene Dartt / Monica Berry /
  Kazuo Tsubota / Jerrold R. Turner /
  Driss Zoukhri)
- **Stem Cell and Proteomics**
  (*Frank Oppenheim* / *David Quissell* /
  Sem Phan / Reen Wu / David Wong)
- **Molecular Mechanisms of Secretory**
  Granule Biogenesis and Acinar
  Cell Secretion
  (*Curtis Okamoto* / *Gary A. Weisman* /
  Wanjin Hong / John A. Williams /
  Sarah Hamm-Alvarez / Sharon Tooze)
- **Salivary Signaling and Development**
  (*Matt Hoffman* / *Shmuel Muallem* /
  Deepak Srevistava / Randall Moon /
  Mu-Ming Poo)
- **Signalplexes and Platforms**
  (*James Melvin* / *James Turner* /
  Carole Liedtke / Sharon L. Milgram /
  Zijian Xie / Stephen P. Soltoff)
- **Salivary Cell Death and Adaptive**
  Responses
  (*Seunghee Cha* / *Kirsten Limesand* /
  Mary Reyland / Bruce Baum /
  Andrei V. Gudkov / Steve Anderson)
- **Transport Processes**
  (*David Cook* / *J. Kevin Foskett* /
  David Cook / Eric Delpire / Indu Ambudkar /
  Michael Cahalan / Peter Thorn)
- **The Grand Finale: Frontier and Future**
  (*David Ann* / *David Yule* /
  Katsuhiko Mikoshiba / Peter Agre)

SIGNAL TRANSDUCTION
WITHIN THE NUCLEUS
CROWNE PLAZA
VENTURA, CA
MAR 25-30, 2007
JOHN YORK, CHAIR
SUSAN WENTE &
NAL DIVECHA, CO-VICE CHAIRS

- **Nucleocytoplasmic Signaling I**
  (Gerald Crabtree / Anjana Rao /
  Martha Cyert / Reuben Shaw / *John York*)
- **Nuclear Envelope Dynamics**
  (Martin Hetzer / *Ulrike Kutay* /
  Michael Rout / Robert Goldman /
  Colin Stewart / Sandra Marmiroli)
- **Phospholipid Signaling**
  (Susan Henry / Jeremy Thorner /
  Nullin Divecha / Zoya Avramova)
- **Chromatin Modification**
  (*Jerry Workman* / Rui-Ming Xu /
  Ali Shilatifard / Or Gozani /
  Joanna Wysocka / Paolo Sassone-Corsi)
- **Nucleocytoplasmic Signaling II**
  (*Dan Gottschling* / Marta Miaczynska /
  Randall Kaufman / Phil Majerus /
  Vytas Bankaitis)
- **Activation Of RNA Synthesis/Export**
  (*Susan Wente* / Adolfo Saiardi /
  Erin O'Shea / Trevor Archer /
  Kristen Lynch / David Spector)
- **Signaling to DNA Damage Response**
  (*Karlene Cimprich* / Xuetong (Snow) Shen /
  Aziz Sancar)
- **Nuclear Organization**
  (Laura Rusche / Leonard Guarente /
  Pamela Silver / Orna Cohen-Fix /
  Gary Stein / Jonathan Widom)
- **Nucleocytoplasmic Signaling III**
  (*Hitoshi Yagisawa* / Lucio Cocco /
  Dan Raben / Thomas Brock)

SUPRAMOLECULES & ASSEMBLIES,
CHEMISTRY OF
IL CIOCCO
LUCCA (BARGA), ITALY
MAY 6-11, 2007
DIRK KURTH & JOHN TEXTER, CO-CHAIRS
MATTHEW TIRRELL, VICE CHAIR

- **Building Recognition**
  (*Dirk Kurth* / *John Texter* / Toyoki Kunitake /
  Jean-Marie Lehn)
- **SupraParticle Architecture**
  (*Eric Kaler* / Alphons van Blaaderen /
  Orlin Velov)
- **Nanoparticle Compounds**
  (*Donald Fitzmaurice* / Christopher B. Murray)
- **Supramolecular Sensors**
  (*Ijeoma Uchegbu* / Mathias Brust /
  Uwe Sleytr)
- **Electrical & Optical Assemblies**
  (*Patricia Macguiggan* / *Cherie Kagan* /
  Dimitris Tsoukalas)
- **Molecular & Polymer Modification for**
  Assembly
  (*Qun Hoa* / Vince Rotello)
- **Layer-by-Layer Assembly**
  (*Karin Caldwell* / Gero Decher /
  Helmuth Moewald)
- **Supramolecular Photonics and Computing**
  (*Beatrice Juarez* / Eugenia Kumacheva /
  Tadashi Kawazoe)
- **Assembly on Different Length Scales**
  (*Katherina Landfester* / Nick Kotov)
- **Particle-Based Functional Materials**
  (*Heiko O. Jacobs* / Malcolm Green /
  Paul Alivisatos)
- **Biomimetic Crystallization**
  (*Joanna Aizenberg* / Stephen Mann /
  Markus Antonietti)
- **Supramolecular States of Matter**
  (*Maria Santore* / Emmanuel Giannelis)
- **Sticking Things Together**
  (*Matt Tirrell* / Peter Ma / Jacob Israelachvili)

TEMPERATURE STRESS IN PLANTS
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
JAN 21-26, 2007
ELIZABETH VIERLING &
KAZUKO YAMAGUCHI-SHINOZAKI, CO-CHAIRS
RAY BRESSAN &
HERIBERT HIRT, CO-VICE CHAIRS

- **Temperature Control of Flowering**
  (*Jian-Kang Zhu* / Caroline Dean)
- **Genomic Responses to Stress**
  (*Michael Thomashow* / Jian-Kang Zhu /
  Feng Qin / Luigi Cattivelli /
  Kyonoshin Maruyama)
- **Metabolism**
  (*Charles Guy* / Ikuo Nishida / Oliver Fiehn /
  Lloyd Sumner)
- **Signalling**
  (*Heribert Hirt* / Ron Mittler / Robert Hill /
  Asa Strand / Anthony Hall)
- **Photosynthesis**
  (*Asa Strand* / Itzhak Kurek /
  Yoshitaka Nishiyama)
- **Cold Responses in Crop and**
  Natural Systems
  (*Ron Mittler* / Eric Stockinger /
  Gordon Gray / Alison Kermode / Sally Aitken)
- **Membranes and Oxidative Stress**
  (*Kazuko Yamaguchi-Shinozaki* /
  Matsuo Uemura / Shigeru Shigeoka)
- **Crop Improvement**
  (*Eric Stockinger* / Yvan Fracheboud /
  Matthew Reynolds / Cory Christensen /
  Ju-Kon Kim)
- **Enzyme Adaptation to Cold**
  (*Elizabeth Vierling* / Tony Collins)

VASCULAR CELL BIOLOGY
FOUR POINTS SHERATON: HARBORTOWN
VENTURA, CA
FEB 11-16, 2007
BRADFORD BERK, CHAIR
MICHAEL SIMONS, VICE CHAIR

- **Extracellular Matrix Signaling to the**
  Vasculature
  (*Martin Schwartz* / Eleni Tzima /
  George Davis / Federico Bussolino /
  Ragu Kalluri)
- **Apoptosis in Vascular Disease**
  (*Elisabeth Nabel* / Alain Tedgui /
  Slava Korshunov / Ira Tabas / M.J. Kaplan)
- **Vascular Cell Differentiation**
  (*Karen Hirschi* / Gary Owens /
  Per Lindahl / Eli Keshit)
- **Vascular Tube Formation**
  (*George Davis* / Brent Weinstein /
  Donald Ingber / Donald McDonald /
  Mark Krasnow)
- **Endothelial Cell Junctions and**
  Permeability
  (*Radu Stan* / David Cheresh /
  Masahiro Murakami / Vicki Bautch /
  Tanya Mayadas)
- **Immunology of the Vasculature**
  (*Alain Tedgui* / Gwendalyn Randolph /
  Stephen Schwartz / Ralph Kelly)
- **Signal Transduction and Integration**
  (*Gary Gibbons* / Randolph Patterson /
  John Quackenbush / Mark Ginsburg)

Mammalian Cell Colony Counting

The GelCount is an automated mammalian cell colony counting system for counting non-adherent type colonies growing in three-dimensional media such as soft agar and methyl cellulose. GelCount is aimed at researchers using stem cell assays or clonogenic cell-survival (colony-forming) type assays in both basic scientific research and drug discovery. By combining high-resolution, high depth-of-field scanning with innovative digital image processing, GelCount provides a cost-effective solution to the difficult, subjective, and labor-intensive task of manually counting colonies and spheroids in suspension media. GelCount can rapidly detect and count both stained and unstained colonies down to 50 μm diameter. GelCount can simultaneously analyze up to four multi-well plates using a proprietary, multi-thread aware algorithm capable of detecting both diffuse and overlapping colonies and of differentiating real colonies from debris and bubbles.

Oxford Optronix For information +44 1235 821 803 www.oxford-optronix.com

Sequence Analyzer

The HyperSeq system makes use of reconfigurable computing technology to provide the power of 584 computers in a single rack-mounted server. The system is capable of producing DNA sequence alignments results using the Smith-Waterman algorithm at 125 billion cell updates per second. A web interface allows data submission and result retrieval from any machine with an Internet browser. The system provides a turnkey solution for life science researchers working in the field of genomic analysis. Based on field programmable gate array technology, the HyperSeq can be customized to suit a wide variety of algorithms that are computationally or data intensive.

Adaptive Genomics For information 540-552-2700 www.adaptivegenomics.com

Long DNA Kits

The MasterAmp Extra-Long PCR (polymerase chain reaction) Kit enables accurate one-step amplification of DNA sequences from 20 kb to 40 kb in an easy-to-use optimization format. The kit includes the MasterAmp Extra-Long DNA Polymerase Mix along with nine MasterAmp Extra-Long PCR 2X PreMixes with dNTPs, buffer, and varying amounts of $MgCl_2$, along with MasterAmp PCR Enhancer (with betaine).

Epicentre Biotechnologies For information 800-284-8474 www.EpiBio.com/extra-long.asp

Protein Purification Kits

Nunc ProPur Kits provide total protein purification from initial fractionation to final polishing steps in yields typically associated with a gravity drip column, but with the speed of a spin column. Users can purify proteins tagged with IgG, IgA, and histidine in 20 to 50 minutes. Based on affinity chromatography, the kits make use of protein G, protein A, or metal chelate (IMAC) resin chemistries pre-packed in ready-to-use spin columns. Three formats are available. ProPur Mini Kits feature microcentrifuge tubes with working volumes of 0.65 ml and a binding capacity of up to 1 mg protein. ProPur Midi Kits feature 50-ml centrifuge tubes with working volumes of 20 ml and a binding capacity up to 20-mg protein. ProPur Vac Kits make use of vacuum-driven columns for purifying IgG and IgA from large volumes of dilute cell culture supernatant.

Nalge Nunc International For information 800-446-2543 www.nalgenunc.com

Image Sharing Software

NetCam, a feature of Olympus MicroSuite FIVE imaging software, allows the microscope user to share images easily with colleagues in other geographic locations. It is designed for use with a number of cameras, including the Olympus DP71, DP70, and DP20, as well as many other popular cameras. NetCam makes use of TCP/IP (transmission control protocol/Internet protocol) to broadcast a live image over the Internet via an assigned static IP address. Up to 50 remote client computers can simultaneously log on and view a live or captured image using a standard web browser. The primary user can manually or automatically adjust the microscope and camera parameters; capture, annotate, and send images; and control access by remote users.

Olympus America For information 800-455-8236 www.olympusamerica.com/microscopes

Sample Storage Technology

A new room-temperature sample storage system eliminates the need for keeping biological samples cold or frozen. The system includes the SampleMatrix dry storage medium, SampleGard sample storage and transportation system, and SampleWare organizational and retrieval software. Together, these products allow biological samples to be easily stored, transported, and recovered at the bench without the need for cold storage. SampleMatrix is a dissolvable compound that stabilizes biological samples at room temperature. This synthetic polymer dissolves within minutes during sample hydration and allows total recovery without degradation or loss of activity. SampleGard sample storage and transportation system features a 96-well plate that comes preloaded with SampleMatrix medium, so it is ready to use in all high-throughput applications. The system allows for fast storage and retrieval, with less than two minutes hands-on time. Samples do not require purification and are ready to assay in just 15 minutes.

Biomatrica For information 866-DRY-MATRIX www.biomatrica.com

Newly offered instrumentation, apparatus, and laboratory materials of interest to researchers in all disciplines in academic, industrial, and government organizations are featured in this space. Emphasis is given to purpose, chief characteristics, and availability of products and materials. Endorsement by *Science* or AAAS of any products or materials mentioned is not implied. Additional information may be obtained from the manufacturer or supplier by visiting www.science.labvelocity.com on the Web, where you can request that the information be sent to you by e-mail, fax, mail, or telephone.

POSITIONS OPEN

ROSALIND FRANKLIN UNIVERSITY OF MEDICINE AND SCIENCE

ASSISTANT/ASSOCIATE PROFESSOR
Mebrane Protein Structural Biology

As part of a University-wide initiative, the Department of Biochemistry and Molecular Biology (BMB) continues to undergo significant expansion and invites applications for a tenure-track Assistant or Associate Professor in the area of membrane protein structural biology. We seek candidates employing cutting-edge biophysical techniques that will provide fundamental insight into the structure-based mechanisms of membrane proteins. Although preference will be given to candidates using X-ray crystallography or cryo-electron crystallography, outstanding candidates employing other biophysical approaches are also encouraged to apply. BMB is a well-funded active Department that enjoys strong University commitment to development of membrane protein structural biology. In addition to faculty recruitment in this area, the University commitment includes recent development of the Rosalind Franklin Structural Biology Laboratories (consisting of state-of-the-art facilities for X-ray diffraction, mass spectrometry/proteomics, and electron paramagnetic resonance) and a biophysical instrumentation facility, as well as access to the nearby American Physical Society via participation in the Southeast Regional Collaborative Access Team beamline consortium. Candidates at the Assistant Professor level must have outstanding research potential and a commitment to excellence in teaching, whereas applicants at the Associate Professor level must demonstrate outstanding research accomplishment including national recognition and extramural funding, as well as a track record in graduate training. The successful candidate will receive a highly competitive salary, an attractive startup package and space, and is expected to develop or maintain an externally funded research program, as well as teach at the medical and graduate school levels. Further information about the Department can be viewed at **website: http://www.rosalindfranklin.edu/cms/biochem.** Interested applicants should submit their curriculum vitae, a two-page summary of research interests, copies of representative publications, and the names of at least three references to: **Dr. Ronald S. Kaplan, Chair, Department of Biochemistry and Molecular Biology, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Road, North Chicago, IL 60064,** or as an attached document to **e-mail: ronald.kaplan@rosalindfranklin.edu.** Review of applications will begin immediately and will continue until the position is filled. *Rosalind Franklin University of Medicine and Science is an Equal Opportunity/Affirmative Action Employer.*

JUNIOR FACULTY POSITION
Pharmacology and Physiology

The Department of Pharmacology and Physiology at the University of Medicine and Dentistry of New Jersey-New Jersey Medical School is seeking applicants for a research faculty position at the **ASSISTANT PROFESSOR** level. Applicants should have a Ph.D. or M.D., should have demonstrated excellence in research, and expertise in molecular or cellular neuroscience. The successful candidate will work on a research team investigating metabolic sensing in the brain using fluorescence imaging, electrophysiology, and molecular biology approaches.

Send resume including names of at least three references and a description of research interests, to: **Andrew P. Thomas, Ph.D., The Thomas P. Infusino Endowed Chair, Professor and Chair of Pharmacology and Physiology, New Jersey Medical School of UMDNJ, 185 S. Orange Avenue, MSB H609, P.O. Box 1709, Newark, NJ 07101-1709.** *University of Medicine and Dentistry of New Jersey is an Affirmative Action/Equal Opportunity Employer (Minorities/Females/Persons with Disabilities/Veterans) and is a member of the University Health Systems of New Jersey.*

POSITIONS OPEN

The School of Life Sciences at the University of Nevada Las Vegas (UNLV) **(website: http://biology.unlv.edu/)** invites applications for a full-time, nine-month, tenure-track **ASSISTANT PROFESSOR** with research expertise in functional morphology/biomechanics, commencing fall 2007. Individuals who study structure-function relationships via integration of modern physiological, evolutionary, developmental, engineering and/or computational approaches are encouraged to apply. The successful candidate will be expected to develop a vigorous, extramurally funded research program, excel in teaching and mentoring the Department's B.S., M.S., and Ph.D. programs, and provide service to the Department, College, University, and the profession. While the research model is open to any animal system, the successful candidate will be expected to teach comparative vertebrate anatomy and other courses within his/her specialty in the physiology curriculum. The School of Life Sciences has 28 full-time faculty representing the breadth of the biological disciplines. This position will add to a leading program in integrative and comparative physiology and is supported by excellent core facilities and a competitive laboratory space. A Ph.D. in a life science field from an accredited College or University, postdoctoral experience, and a record of creative and significant research in animal functional morphology/biomechanics is required. Salary is competitive and contingent on the labor market and upon funding. Application materials must be submitted via the UNLV online application portal at **website: https://hrsearch.unlv.edu** and include a cover letter, curriculum vitae, and in the Other Docs field, a single document including proposed research plans and teaching interests, along with citations of at least three key publications. For assistance with UNLV's online applicant portal, contact **Jen Feldmann** at **telephone: 702-895-3886** or **e-mail: hrsearch@unlv.edu.** Three letters of recommendation should be sent to **Dr. Stephen Roberts (e-mail: stephen.roberts@unlv.edu, telephone: 702-895-4471), Functional Morphology/Biomechanics Search Committee Chair, School of Life Sciences, University of Nevada Las Vegas, 4505 Maryland Parkway, Las Vegas, NV 89154-4004.** To receive full consideration, application materials should be received by November 15, 2006.

UNLV is an Affirmative Action/Equal Opportunity Educator and Employer committed to excellence through diversity.

ASSISTANT PROFESSOR
Cell Biology/Microbiology
Carleton College

The Department of Biology invites applications for a Tenure-Track position starting fall 2007. We seek candidates who have research and teaching interests in microbiology and cell biology. We are especially interested in applicants who use modern molecular approaches and/or computational techniques in their research. Teaching responsibilities include: upper-level courses in cell biology and microbiology, team-teaching in the introductory biology sequence, and advanced laboratory offerings.

Candidates should be committed to excellence in undergraduate teaching in a liberal arts environment, and dedicated to developing an active research program that engages students. We are particularly interested in applicants who will strengthen the departmental commitment to students from underrepresented groups in the biological sciences. Candidates must have a Ph.D. in biology or a related field, and postdoctoral experience is preferred. Please send letter of application, curriculum vitae, a statement of teaching philosophy and research plans, and three letters of reference to: **Professor Matthew Rand, Department of Biology, Carleton College, Northfield, MN 55057-4025.** Application deadline is December 1, 2006.

Carleton College is an Affirmative Action/Equal Opportunity Employer. We are committed to developing our faculty to better reflect the diversity of our student body and American society. Women and members of minority groups are strongly encouraged to apply.

Faculty Positions
Transferring Technology

Intellectual property and technology transfer play important roles in today's science. A scientist's career can change dramatically through patents, which can spawn companies or funds for research. Moreover, some scientists create exciting careers by moving from the bench to a technology transfer office in academics, government, or industry. BY MIKE MAY


FRED FARINA

Science usually depends partly on money. In the past, people generally thought of inventors and engineers as the ones with commercial aspirations. For example, Thomas Edison focused intently on patenting his work—earning 1,093 patents during his career. Now, many academic scientists patent their discoveries, and major universities sprout startups on a regular basis. To survive in today's commercial environment, scientists need help with legal issues and patent applications.

Discoveries often spur discussions of intellectual property, or IP. It represents a legal framework to stimulate innovation. Anne M. Schneiderman, a patent attorney who runs her own firm in Ithaca, New York, explains that IP covers many classes: patents, trademarks, and trade secrets, or proprietary information inside a company. "These categories of IP can be viewed like real property," she says. "In the case of patents, you actually get a real deed that describes the boundaries of the IP."

A scientist seeks a patent to protect the possible commercial applications of a discovery. Fred Farina, assistant vice president in the Office of Technology Transfer at the California Institute of Technology, says, "A patent gives its owner a time-limited monopoly, so they can commercially exploit their patented invention."

Not just anything, however, can be patented. Milind Sant, business development director in the Office of Technology Management at Washington University in St. Louis, says, a patentable concept must be new, and it must not be obvious. Moreover, he says that the concept should be commercially useful and include some work that shows its potential. "This enhances the value of a patent application," he says.

In some cases, an organization—say, a university—possesses the means to invent new ideas but not to commercialize them. That's where technology transfer picks up the process. Farina describes technology transfer as "taking an invention that is a concept and moving it to the marketplace as a product or service."

In addition to monetary advances, IP and technology transfer can provide public benefits. "If someone invents something that could help people," says Andrea Schievella, a technology licensing officer at the Massachusetts Institute of Technology, "what a ter- CONTINUED »

California Institute of Technology
http://www.caltech.edu

Law Offices of Anne M. Schneiderman, Ph.D.
http://www.schneidermanlaw.com

Massachusetts Institute of Technology
http://web.mit.edu

Washington University in St. Louis
http://www.wustl.edu

Faculty Positions

rible shame it is if no one does anything with it." She gives this scenario: "What if somebody is collaborating with a medical school and comes up with compounds that fight cancer? If you don't patent those and have someone license them, no company will ever develop them."


MILIND SANT

What Scientists Should Know

The interest in IP and technology transfer seems on the rise among younger scientists. "After talking to a number of them," says Farina, "I find that many have the desire to do a startup of some sort. So they are more aware of IP and technology transfer than scientists were a decade or so ago." Nonetheless, many scientists do not think along IP lines. "Some scientists still just want to publish results and give the knowledge to the public domain," says Sant, "but many of the ideas that get published don't get developed." Turning an idea into a public benefit requires a commercial angle, and that can slip away without patent protection.

How much a scientist needs to know about IP and technology transfer depends on who is being asked. Farina, for example, believes that scientists do not need to know all of the intricacies of these areas. Instead, he thinks that researchers can rely largely on a university's technology transfer office. If someone does not protect discoveries, though, trouble can arise. "We have to fight problems caused by scientists who are not aware of IP, and they publish too soon, which can compromise their rights."

A patent, though, is not the only way to generate a product from a new idea. "Sometimes, a group prefers to keep something as a trade secret instead of applying for a patent," Schneiderman says. "A patent is a bargain with the federal government in which the government grants you the right to have a monopoly on your invention for a limited amount of time—generally 20 years from the date of filing the patent application—in exchange for divulging everything about your invention to the public." The federal government, however, does not enforce the monopoly right; the inventor, patent owner, or licensee bears the burden of enforcement. In some cases, companies prefer to guard the secret, use it, and hope that no one else ever discovers it.

The patenting process varies among universities, but here's an example. It usually starts with an invention disclosure form—basically a description of the invention or concept. Sant says, "Ours includes information about how the invention differs from existing technology and which companies might be interested." Then, a scientist interacts with the technology transfer office to move ahead with the process. The process also varies between countries. In applying for a patent in the United States, Schneiderman explains, a scientist can take up to a year after presenting information at a meeting. "If you wish to apply for a patent in most other countries," she says, "you cannot have released anything publicly before filing."

Also, a scientist might turn to patenting for more than commercial reasons. For instance, science can breed businesses that fund more science. Sant says, "Licensing revenues from a patent come back to the lab so that scientists can do more research."


ANDREA SCHIEVELLA

Getting the Right Stuff

Many universities provide training on IP and technology transfer. At the California Institute of Technology, the technology transfer office runs regular seminars on these areas. At Washington University in St. Louis, the Office of Technology Management gives presentations and offers an eight-week course that covers issues related to startups. Also, a scientist can just arrange a meeting with a technology transfer officer.

Schneiderman also points out that some technology transfer offices post information on their websites, including invention disclosure forms and instructions on protecting a discovery. Scientists can also learn more from organizations, such as the Association of University Technology Managers (http://www.autm.net), the World Intellectual Property Organization (http://www.wipo.int), and the United States Patent and Trademark Office (http://www.uspto.gov), which provides resources for inventors (http://www.uspto.gov/web/offices/com/iip/index.htm).

In thinking of a patent, though, scientists should not see it as a roadblock to publishing. "We do not hold up publication," says Schievella. "We work with you to get out the results but to protect them, too."


ANNE M. SCHNEIDERMAN

A Career Transfer

IP and technology transfer professionals come from many backgrounds. Farina started as an electrical engineer. Then, he sat for the patent agent exam. A patent agent can put together a patent and push it through the process. In cases of patent litigation—enforcing the rights of a patent, for example—a patent attorney takes control. Either way, says Farina, "People usually just fall into this kind of work." Coming from a scientific background, though, really helps. "It is actually required to sit for the patent bar exam," says Farina.

Nonetheless, a background in business also plays a fundamental role. Schievella combined science and business to work in this field. She earned a Ph.D. in cellular and molecular biology, completed a postdoc, and then worked in industry. She turned to IP and technology transfer when a conference sparked her interest. Sant followed a similar course. After earning his Ph.D. in organic chemistry, he worked in industry as a medicinal chemist. Then, he moved to business development and earned an M.B.A. Schneiderman also came from a scientific background—nearly 20 years as a neurobiologist. Then, she went to law school, and she now focuses on biotechnology. "My scientific background is very important in reading and understanding the research behind a patent application," she says. In addition, she points out that jobs for patent attorneys rise and fall with good and bad times for the technology industry. "Still, there are far more jobs for patent attorneys than there are for university researchers," she says.

Mike May (mikemay@mindspring.com) is a publishing consultant for science and technology based in the state of Minnesota, U.S.A.

WESTERN UNIVERSITY OF HEALTH SCIENCES
COLLEGE OF OSTEOPATHIC MEDICINE OF THE PACIFIC

Daljit and Elaine Sarkaria Endowed Professorship Parkinson's Disease and Aging Related Motor Disorders

The faculty of Western University of Health Sciences, College of Osteopathic Medicine of the Pacific invites applications and nominations for the second Daljit & Elaine Sarkaria endowed Professor in Neuroscience. The Sarkaria Professorship is a full-time tenured appointment at the rank of Professor or Associate Professor. Applicants must have a doctorate in an appropriate field with an outstanding record of obtaining extramural grants and publications. Candidates are also expected to be excellent at teaching and mentoring junior colleagues. The first Sarkaria Professorship focuses on research and teaching in the area of Alzheimer's disease and other aging related dementias. Candidates for the second professorship are expected to carry out research in the field of Parkinson's disease and associated movement disorders. The successful candidate is expected, together with the first Sarkaria professor, to establish a strong basic and/or clinical research program in neurodegenerative diseases as part of the University's rapidly growing research program. In addition to the endowment for research support, the successful candidate will receive significant start-up funds, abundant laboratory space and competitive salary.

Applicants should submit a cover letter expressing their interest, statements of research activity and teaching philosophy along with curriculum vitae, current support, and contact information of three potential references to:

Nissar A. Darmani, Ph.D., Chair,
Department of Basic Medical Sciences
Western University of Health Sciences
College of Osteopathic Medicine of the Pacific
309 E. Second Street
Pomona, CA 91766-1854

Email Address: ndarmani@westernu.edu

ANATOMY RESEARCH AND TEACHING FACULTY POSITIONS

The Western University of Health Sciences has committed itself to a far reaching strategic plan to significantly expand the five established colleges: College of Osteopathic Medicine of the Pacific, College of Graduate Nursing, College of Pharmacy, College of Allied Health Professions and College of Veterinary Medicine. The University has initiated the construction of a new 250,000 sq. ft. medical teaching and research facility that will house the College of Osteopathic Medicine as well as the future colleges of dentistry, podiatry, optometry and graduate studies. The new building will include 50,000 square feet of space dedicated to research. The department of Anatomy in the College of Osteopathic Medicine of the Pacific (COMP) will significantly increase faculty numbers in the areas of research and innovation in medical education to serve the new colleges. We are seeking Ph.D. anatomy candidates for tenure track faculty positions at the level of Assistant, Associate or Full Professor to **EITHER**:

- **Participate in research and limited teaching.** Competitive salary, significant start-up support and abundant laboratory space will be offered. The successful applicants are required to already have obtained extramural funding from major federal or other granting agencies (Associate or Full Professor) or have successfully completed a postdoctoral program with strong potential to obtain grants (Assistant Professor). The University will allow ample protected time for research goals.
- **Health Professions Education:** Teach Gross Anatomy, Histology, and/or Neuroanatomy to students in one of our programs. The successful applicants must have several years of experience in teaching in the anatomical sciences. Experience with innovative curriculum development and publications that will lead to the attainment of extramural educational grants are required.

Applicants should submit a cover letter expressing their interest, statements of research activity and teaching philosophy along with curriculum vitae, current support, and contact information of three references to:

James May, Ph.D., Chair, Department of Anatomy
Western University of Health Sciences
College of Osteopathic Medicine of the Pacific
309 E. Second Street
Pomona, CA 91766-1854

Email Address: jfmay@westernu.edu

BIOCHEMISTRY RESEARCH AND TEACHING FACULTY POSITIONS

The Western University of Health Sciences has committed itself to a far reaching strategic plan to significantly expand the five established colleges: College of Osteopathic Medicine of the Pacific, College of Graduate Nursing, College of Pharmacy, College of Allied Health Professions and College of Veterinary Medicine. The University has initiated the construction of a new 250,000 sq. ft. medical teaching and research facility that will house the College of Osteopathic Medicine as well as the future colleges of dentistry, podiatry, optometry and graduate studies. The new building will include 50,000 square feet of space dedicated to research. The department of Basic Medical Sciences in the College of Osteopathic Medicine of the Pacific (COMP) will significantly increase faculty numbers in the areas of research and innovation in medical education to serve the new colleges. We are seeking Ph.D. biochemists for tenure track faculty positions at the level of Assistant, Associate or Full Professor to **EITHER**:

- **Participate in research and limited teaching.** Competitive salary, significant start-up support and abundant laboratory space will be offered. The successful applicants are required to already have obtained extramural funding from major federal or other granting agencies (Associate or Full Professor) or have successfully completed a postdoctoral program with strong potential to obtain grants (Assistant Professor). The University will allow ample protected time for research goals.
- **Medical Education:** Teach basic and clinical medical biochemistry to osteopathic medical students. The successful applicants must have several years of experience in teaching medical biochemistry. Experience with innovative curriculum development and publications that will lead to the attainment of extramural educational grants is required.

Applicants should submit a cover letter expressing their interest, statements of research activity and teaching philosophy along with curriculum vitae, current support, and contact information of three potential references to:

Nissar A. Darmani, Ph.D., Chair,
Department of Basic Medical Sciences
Western University of Health Sciences
College of Osteopathic Medicine of the Pacific
309 E. Second Street
Pomona, CA 91766-1854

Email Address: ndarmani@westernu.edu

IMMUNOLOGY/MICROBIOLOGY RESEARCH AND TEACHING FACULTY POSITIONS

The Western University of Health Sciences has committed itself to a far reaching strategic plan to significantly expand the five established colleges: College of Osteopathic Medicine of the Pacific, College of Graduate Nursing, College of Pharmacy, College of Allied Health Professions and College of Veterinary Medicine. The University has initiated the construction of a new 250,000 sq. ft. medical teaching and research facility that will house the College of Osteopathic Medicine as well as the future colleges of dentistry, podiatry, optometry and graduate studies. The new building will include 50,000 square feet of space dedicated to research. The department of Basic Medical Sciences in the College of Osteopathic Medicine of the Pacific (COMP) will significantly increase faculty numbers in the areas of research and innovation in medical education to serve the new colleges. We are seeking Ph.D. immunologists/microbiologists for tenure track faculty positions at the level of Assistant, Associate or Full Professor to **EITHER**:

- **Participate in research and limited teaching.** Competitive salary, significant start-up support and abundant laboratory space will be offered. The successful applicants are required to already have obtained extramural funding from major federal or other granting agencies (Associate or Full Professor) or have successfully completed a postdoctoral program with strong potential to obtain grants (Assistant Professor). The University will allow ample protected time for research goals.
- **Medical Education:** Teach basic and clinical medical immunology/microbiology to osteopathic medical students. The successful applicants must have several years of experience in teaching medical immunology/microbiology. Experience with innovative curriculum development and publications that will lead to the attainment of extramural educational grants is required.

Applicants should submit a cover letter expressing their interest, statements of research activity and teaching philosophy along with curriculum vitae, current support, and contact information of three potential references to:

Nissar A. Darmani, Ph.D., Chair,
Department of Basic Medical Sciences
Western University of Health Sciences
College of Osteopathic Medicine of the Pacific
309 E. Second Street
Pomona, CA 91766-1854

Email Address: ndarmani@westernu.edu

Western University of Health Sciences takes affirmative action to ensure equal employment opportunity.

POSITIONS OPEN

DIRECTOR
Stanley S. Scott Cancer Center
Louisiana State University Health Sciences Center
New Orleans

The Louisiana State University Health Sciences Center (LSUHSC), School of Medicine in New Orleans, Stanley S. Scott Cancer Center, is accepting applications for the Director of the Cancer Center. The position requires an M.D., Ph.D., or both, with combined M.D., Ph.D. degrees preferred. Preference will be given to candidates with experience in working within or in developing a successful plan for an NCI designated cancer center. The ideal incumbent must demonstrate scholarly experience as evidenced by academic accomplishments, publications, service on national study sections, service on editorial boards, and a track record of extramural research funded through NCI or other NIH funding mechanisms. Administrative experience with building either cancer research programs or cores in an academic setting is preferred. The incumbent should qualify for appointment at the level of Professor. A track record in basic, translational, epidemiological, and/or clinical research is required. Knowledge of current clinical oncology operations in relation to academic medicine will be viewed positively. The ideal candidate should have demonstrated ability in developing translational research from the basic scientific observations to clinical trials or clinically relevant research.

The incumbent will be appointed to the appropriate clinical department and will be a member of the Stanley S. Scott Cancer Center. Also the incumbent will be Co-Director of the Louisiana Cancer Research Consortium of LSU and Tulane. Please send curriculum vitae including current grant funding, a brief cover application letter detailing professional interests and goals, and the names of three references to: **Bernard Wan, Dean's Office, School of Medicine, 533 Bolivar Street, New Orleans, LA 70112** with an **e-mail: bwan@lsuhsc.edu.**

LSUHSC is an Affirmative Action/Equal Opportunity Employer.

MICROBIOLOGIST. ASSISTANT PROFESSOR, tenure-track, Ph.D. required. Position will begin in September 2007. The candidate is expected to supervise undergraduate research and to teach introductory biology classes, introduction to research, microbiology, and molecular biology. The applicant will have the opportunity to develop courses in his/her specialty and will be expected to develop a research program accessible to undergraduates as well as maintain his/her own research. Candidates should submit their curriculum vitae, statements of teaching philosophy and research interests, and three letters of recommendation to: **Dr. Stuart Allison, Biology Department, Knox College, Galesburg, IL 61401.** Review of applications will begin on December 1, 2006, and continue until the position is filled. For more information about biology and Department facilities at Knox, check **website: http://www.knox.edu/biology.xml.**

In keeping with its 170-year commitment to equal rights, Knox College particularly welcomes applications from women and members of other historically underrepresented groups.

The Department of Chemistry at the University of Southern California (USC) invites applicants for a tenure-track position at the level of **ASSISTANT or ASSOCIATE PROFESSOR** in inorganic or inorganic/biological chemistry, to start in the fall of 2007. A Ph.D in chemistry is required. We are interested in candidates in all areas of inorganic chemistry, including nanoscience, bioinorganic/biomaterials/biomedical sciences, energy sciences, and related interdisciplinary fields. Interested candidates should send curriculum vitae, a detailed description of research plans, and three letters of recommendation to: **Inorganic Chemistry Search Committee, Department of Chemistry, University of Southern California, Los Angeles, CA 90089-0744.** In addition, PDF versions of the curriculum vitae and research plans should be e-mailed to **e-mail: inorgsearch2006@chemmail.usc.edu.** We will begin evaluation of applications as they become complete. *USC is an Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

UW Medicine
SCHOOL OF MEDICINE

OPEN FACULTY POSITIONS

The Department of Genome Sciences at the University of Washington is continuing a major expansion under its Chair, **Dr. Robert Waterston**, and will move into the new Foege Building in fall 2006. Research in the Department encompasses both genetic and genomic analysis of humans and model organisms. Our Department also has a significant focus in technology development and in computational biology across all levels including sequence, expression, proteomics, network, and genetic analysis. The Department invites applications in any of these areas for two faculty positions at the rank of **ASSISTANT PROFESSOR**, although exceptional candidates may be considered at the rank of **ASSOCIATE or FULL PROFESSOR.** Both positions involve establishing an active research program as well as teaching duties. Applicants should hold a Ph.D. and/or M.D. degree. Applications will be reviewed upon receipt until December 1, 2006.

Contact:

Dr. Deborah Nickerson
Search Committee Chair
Department of Genome Sciences
University of Washington
P.O. Box 357730
Seattle, WA 98195
E-mail: faculty-search@gs.washington.edu

Candidates should e-mail their curriculum vitae and statement of research and teaching interests, and arrange to have three signed letters of reference sent by mail.

For additional information that may be helpful in preparing an application, see the Department's **website: http://www.gs.washington.edu.**

The University of Washington is building a culturally diverse faculty and strongly encourages applications from women and minority candidates. The University of Washington is an Affirmative Action/Equal Opportunity Employer.

VERTEBRATE BIOLOGIST TENURE-TRACK POSITION

Truman State University invites applications for a tenure-track **ASSISTANT PROFESSOR** position in vertebrate biology, starting August 2007. The successful candidate will have a field-based research program that is attractive to undergraduate and Master's researchers; an organism-level research focus; and expertise in herpetology, ichthyology, or ornithology. Teaching requirements include majors or nonmajors introductory biology, upper level elective course(s), and (possibly) a mid-level core course.

Candidates should be strongly committed to the teacher-scholar model in a liberal arts and sciences institution and to maintaining both quality teaching and an active research program. A research laboratory in our new Science building and competitive startup funds will be provided. To review a more detailed position announcement, please visit **website: http://www.truman.edu/pages/152.asp.** For more information about the University and the Biology Program, please visit **websites: http://www.truman.edu** and **http://biology.truman.edu.**

Candidates should possess a Ph.D. by August 2007. Complete applications include: letter of application; current curriculum vitae; statement of teaching philosophy and commitment to the liberal arts and sciences and student development; statement of research interests and goals; three recent letters of recommendation; and all graduate and undergraduate transcripts (copies acceptable, official copies of graduate transcripts required prior to hiring). All application materials should be sent to: **Dr. Jon Gering, Biology Faculty Search, Division of Science, Truman State University, 100 E. Normal Street, Kirksville, MO 63501-4221, telephone: 660-785-4597.** Review of complete applications will begin November 13, 2006.

Truman is an Equal Employment Opportunity/Affirmative Action/Americans with Disabilities Act Employer.

POSITIONS OPEN

DEPARTMENT CHAIR
Baylor University
Department of Chemistry and Biochemistry

The Department of Chemistry and Biochemistry at Baylor University invites applications and nominations for the position of Department Chair beginning in August 2007. This position will be filled at the **ASSOCIATE or FULL PROFESSOR** rank, and is open to applicants in any area of chemistry or biochemistry.

Baylor University is a private University chartered in 1845 with an enrollment of 14,000 students. The Department of Chemistry and Biochemistry has 16 tenured and tenure-track faculty members along with eight full-time Lecturers, and offers B.A., B.S., M.S., and Ph.D. degrees. The Department currently serves approximately 275 undergraduate majors and 50 graduate students, and occupies a significant portion of the new 500,000 square feet Baylor Sciences Building. Please visit **website: http://www.baylor.edu/chemistry/chairsearch** for further details regarding the Department, Baylor University, and Waco, Texas.

Complete applications should include current curriculum vitae, a description of research interests, and a statement describing the candidate's interests and goals in seeking this position. Applications will be reviewed beginning December 1, 2006. To ensure full consideration an application should be received by January 1, 2007, but applications will be accepted until the position is filled.

Applicants should have a record of high quality research and demonstrated success in obtaining external funding. Previous administrative experience is desirable. The successful applicant will be committed to excellence in both graduate and undergraduate education and be strongly supportive of Baylor's distinctive mission and vision.

Send all materials to: **Dr. Kevin Klausmeyer, Chair Search Committee, One Bear Place 97348, Waco, TX 76798. E-mail: kevin_klausmeyer@baylor.edu.**

Baylor is a Baptist University affiliated with the Baptist General Convention of Texas. *As an Affirmative Action/Equal Employment Opportunity Employer, Baylor encourages minorities, women, veterans, and persons with disabilities to apply.*

ASSISTANT PROFESSOR

An accomplished scientist using biochemical, cellular, immunological, and/or genetic approaches to investigate infectious disease, zoonoses, or host response to infectious agents is sought for a Tenure-Track position (90 percent research, 10 percent instruction) in the Department of Veterinary Molecular Biology (VMB) at Montana State University. We are seeking an individual to complement or expand existing VMB expertise in the study of viral, protozoan, fungal, prion, and bacterial pathogens, as well as host responses against these pathogens. This position is funded by a competitive institutional salary (nine months), technician support, and a generous startup package. VMB is housed in a new research building (occupied in 2003) with state-of-the-art facilities for flow cytometry, cell biology, molecular sciences, and pathogen containment (BSL-3) facilities (completion date: spring 2007). A doctoral degree in a biomolecular discipline and postdoctoral experience are required. The potential to establish or evidence of a competitive, independent research program is required. Interested applicants should send a letter of application, curriculum vitae, selected reprints, a summary statement concerning research plans and grant proposals, and arrange for three letters of reference to be sent to: **Chair, Search Committee, Veterinary Molecular Biology, Montana State University, P.O. Box 173610, Bozeman, MT 59717-3610.** Screening will begin November 27, 2006, and will continue until a suitable applicant is hired. For a full job description and additional information about our Department visit our **website: http://vmb.montana.edu.** *ADA/Equal Opportunity/Affirmative Action/Veterans Preference.*

IRVING JOHNSON DISTINGUISHED PROFESSOR OF MOLECULAR BIOLOGY

The University of Kansas is undergoing a major expansion of the life sciences on the beautiful Lawrence campus. The Department of Molecular Biosciences invites applications for a faculty position at the rank of distinguished professor. The successful candidate will be a molecular biologist who has a well-established, internationally recognized program of research. This person will also participate in teaching and provide service. Required qualifications: a doctorate in the biological or chemical sciences; a distinguished record of research in the field of molecular biology; a commitment to high quality academics; eligibility for appointment as a tenured, distinguished professor; and appropriate authorization to work in the U.S. before employment begins. A competitive salary and start-up package commensurate with this senior appointment will be provided.

For a full position description refer to: **www.molecularbiosciences.ku.edu**. Applicants should submit a cover letter summarizing their qualifications and interest in the position, future research plans, teaching philosophy and/or experience, curriculum vitae and the names and contact information of at least three references in a single PDF file to **molbiosearch@ku.edu** or by mail to: **Linda Wiley, Administrative Associate, Molecular Biology Search, Department of Molecular Biosciences, University of Kansas, 1200 Sunnyside Ave., Room 2034, Lawrence, KS 66045-7534**. Review of applications will begin **January 15, 2007** and will continue until the position is filled.

EO/AA Employer.

FACULTY POSITION IN NEUROSCIENCE

The Department of Molecular Biosciences at the University of Kansas seeks applicants for a tenure-track **ASSISTANT PROFESSOR** in neuroscience. Applicants must have a Ph.D. (or equivalent) and post-doctoral experience. Successful candidates will be expected to develop and maintain an active research program. The application should include a cover letter, curriculum vitae, statements of research and teaching interests, and three letters of reference sent separately to the address below.

To ensure full consideration, complete applications should be received by **December 1, 2006**. The application can be submitted as a single PDF file to **neurosearch@ku.edu**, or by mail to:

Linda Wiley, Administrative Associate
Neuroscience Search
Department of Molecular Biosciences
University of Kansas
1200 Sunnyside Avenue
Room 2034
Lawrence, KS 66045-7534

The expected start date of the position is August 2007. For more information about the Department of Molecular Biosciences, consult our website (**http://www.molecularbiosciences.ku.edu/**).

EO/AA Employer.

University of Heidelberg

The **Faculty of Clinical Medicine Mannheim, University of Heidelberg** offers the position of an

Associate Professor (W3) of Cardiovascular Physiology

The Associate Professorship will be a tenured position. Given a distinguished record of qualifications in all areas of Cardiovascular and Vegetative Physiology, the successful candidate will be appointed as a Section Head at the newly founded Center for Biomedicine and Medical Technology Mannheim (CBTM), Research Division of Vascular Biology and Physiology. Regarding the implementation of the preclinical medical studies at the faculty (MaReCuM), the successful candidate will be responsible for developing and performing the physiological parts of the restructured organ-centered teaching modules in cooperation with the W3-Professorship for Neurophysiology. As an independent principle investigator, the candidate will have special responsibility for enforcing the research mission of the Faculty with a focus on basic cardiovascular research relevant to cardiovascular pathogenesis. He/she is expected to closely collaborate with the joint Aventis Endowed Chair of Vascular Biology and Tumor Angiogenesis of the Faculty and the German Cancer Research Center (DKFZ) Heidelberg and with the Endowed Associate Professorship of Microvascular Biology and Pathobiology of the Faculty and the University Medical Center Mannheim. He/she should actively take part in established and developing research programs of the Faculty in the field of vascular biology such as the European Graduate School "Vascular Medicine" (EU-GRK 880), the Graduate School "Molecular Imaging" (GRK 886) and the Cooperative Transregio Research Grant "Vascular Differentiation and Remodeling" (TRR 23). He/she is furthermore expected to obtain extramural funding by grant applications to non-university funding institutions.

The successful candidate should have high ranking, internationally acknowledged academic qualifications commensurate with the rank of an associate professor with life-time tenure including a PhD or MD/PhD, a distinguished record of original research, mentoring and teaching skills, administrative experience and an understanding of departmental financing in universities. The candidate should be a cooperative personality who will actively master the integrative task of participating in developing and implementing MaReCuM.

The **Faculty of Clinical Medicine Mannheim, University of Heidelberg** offers the position of an

Associate Professor (W3) of Microscopic Anatomy and Histopathology

The Associate Professorship will be a tenured position. Given a distinguished record of qualifications in all areas of microscopic anatomy and histopathology, the successful candidate will be appointed as a Section Head at the Institute of Pathology; the professorship will be closely associated with the newly founded Center for Biomedicine and Medical Technology Mannheim (CBTM) within the Research Division of Molecular Oncology. Regarding the implementation of the preclinical medical studies at the faculty (MaReCuM), the successful candidate will be responsible for developing and performing the anatomical parts of the restructured organ-centered teaching modules under the organizational guidance of the W3-Professorship for Cellular and Molecular Biology and in cooperation with the W3-Professorships for Anatomy and Developmental Biology and for Neuroanatomy. The successful candidate will take special responsibility for the integration of preclinical and clinical studies within the morphological disciplines. As an independent principle investigator, the candidate will have special responsibility for enforcing the research mission of the Faculty with a focus on molecular tumor pathology. He/she is expected to closely collaborate with the W3-Professorship of Pathology and Pathological Anatomy and with the Research Division of Molecular Oncology at the CBTM as well as with the other research groups of the Faculty active in cancer research including the Clinical Cooperative Units with the German Cancer Research Center Heidelberg (DKFZ). He/she is furthermore expected to obtain extramural funding by grant applications to non-university funding institutions.

The successful candidate should be a board certified pathologist and should have high ranking, internationally acknowledged academic qualifications commensurate with the rank of an associate professor with life-time tenure including a PhD or MD/PhD, a distinguished record of original research, mentoring and teaching skills, administrative experience and an understanding of departmental financing in universities. The candidate should be a cooperative personality who will actively master the integrative task of participating in developing and implementing MaReCuM.

The positions are available unlimited. In case that the successful candidate has not been appointed to a professorship position before, State law regulation demands under chapter 50 of the University law to fill the position as a tenure track position for 3 years. Exceptions are possible for candidates from abroad or from non-university institutions if candidates cannot be attracted otherwise. When the position is tenured after the tenure track period, the formal application process need not be repeated.

The University of Heidelberg is an Equal Opportunity/Affirmative Action Employer.

Interested candidates should submit a full CV with copies of certificates, publication list and selected reprints within 4 weeks of publication of this advertisement to **Prof. Dr. Dr. h.c. K. van Ackern, Dean of the Faculty of Clinical Medicine Mannheim, University of Heidelberg, University Medical Center Mannheim, 68135 Mannheim, Germany.**

POSITIONS OPEN

BIOLOGY, THREE TENURE-TRACK FACULTY POSITIONS (integrative physiology, plant development/physiology, aquatic biology). The College of New Jersey (TCNJ) invites applications for three tenure-track faculty positions starting August 2007. Appointments are expected at the **ASSISTANT PROFESSOR** level. Teaching and research are mutually supportive activities at TCNJ. Candidates should be strongly committed to the teacher-scholar model in a primarily undergraduate residential Institution, and to maintaining both high quality teaching and an active and productive research program involving highly motivated undergraduates. A research laboratory in our new Biology Building, which has excellent facilities for research and teaching, and competitive startup funds will be provided. Faculty members also serve as academic advisors and have service responsibilities within the College. For all three positions we seek broadly trained Biologists, who also have potential to collaboratively contribute to interdisciplinary curricular and scholarly efforts within the School of Science and at the College. In addition to the courses listed below, teaching responsibilities may include rotation through a mixed majors/nonmajors introductory course.

(1) Integrative physiology, to teach a junior/senior level course examining the physiological function of animals from the molecular to organ system levels, an upper-level course in area of specialty, and one of our core courses. The candidate will not be expected to teach courses in human anatomy and physiology. Research in any area of animal physiology will be considered.

(2) Plant development or plant physiology, to teach a general botany course, an upper-level plant biology course in the applicant's area of expertise, and one of our core courses. We are especially interested in candidates whose research addresses developmental or physiological questions and who have broad training in plant biology.

(3) Aquatic biology, to teach an upper-level course in the applicant's area of expertise, an organismal biology course, and a course in the core curriculum. The candidate's training and primary research interests should be in the area of aquatic biology, and we are especially interested in candidates with expertise in invertebrate biology.

Candidates should have a Ph.D. postdoctoral experience preferred. Send letter of application; current curriculum vitae; statement of teaching philosophy; statement of research interests and goals; representative publications; all graduate and undergraduate transcripts; and three letters of recommendation by October 27, 2006, to the attention of the **Chair** of the appropriate **Committee (Physiology, Dr. Donald Lovett; Plant Biology, Dr. Janet Morrison; Aquatic Biology, Dr. Curt Elderkin), The College of New Jersey, P.O. Box 7718, Ewing, NJ 08628-0718.** All materials must be received as hard copies via regular mail; electronic materials will not be accepted. For further information about the College, please visit our **website: http://www.tcnj.edu.** *To enrich education through diversity, the College of New Jersey is an Affirmative Action/Equal Opportunity Employer.*

The Department of Ecology and Evolutionary Biology, Tulane University, invites applications for **TWO TENURE-TRACK POSITIONS,** one in wetlands ecology and one in global change biology. One will be filled at the junior level and one at the senior level. We invite applications at all levels for each position. See **website: http://www.tulane.edu/~ebio/News/positions.htm** for more details. Send curriculum vitae, statements of research and teaching interests, selected publications, and names and addresses of three references to: **Wetlands Ecologist Search** or **Global Change Biologist Search, Department of Ecology and Evolutionary Biology, 310 Dinwiddie Hall, Tulane University, New Orleans, LA 70118-5698.** Review of applications will begin December 1, 2006, and the searches will remain open until the positions are filled. These positions are subject to a final University determination on funding. *Tulane University is an Affirmative Action/Equal Employment Opportunity Employer.*

POSITIONS OPEN

Washington University in St. Louis
School of Medicine

IMMUNOLOGY FACULTY POSITIONS at Washington University

The newly created Division of Immunobiology within the Department of Pathology and Immunology invites applications for tenure-track positions at **ASSISTANT, ASSOCIATE, and FULL PROFESSOR** levels. Washington University provides a highly integrative and collaborative environment for basic and translational research in immunology with state-of the-art facilities. Candidates must hold a doctoral-level degree; have postdoctoral experience, and a proven record of accomplishment. Applicants will be expected to develop an independent research program using innovative methodologies in the broadly defined area of immunobiology, focused on developmental, cellular, molecular, or structural questions. Qualified women and minority candidates are especially encouraged to apply.

Applications, preferably in PDF format, should be sent to **e-mail: immunobiology-search@pathology.wustl.edu** and include curriculum vitae, a brief description of past and proposed research, three representative publications, and three letters of recommendation.

Dr. Andrey Shaw, Head
Division of Immunobiology
Department of Pathology and Immunology
Washington University School of Medicine
660 South Euclid, Campus Box 8118
St. Louis, MO 63110

Consideration of completed applications will begin in November 2006.

The Department of Biology at Indiana University of Pennsylvania invites applications for **TWO TENURE-TRACK POSITIONS** in biology in the areas of (1) applied plant ecology and (2) human anatomy or human physiology. These will be at the **ASSISTANT PROFESSOR** level and available August 2007. Doctorate required. We seek energetic, innovative individuals to join a Department undergoing transition as a number of senior faculty members retire. Successful applicants will help build a student-centered learning community, teach introductory as well as specialty-area courses, develop a productive research program that involves both undergraduate and graduate students and commit themselves to the teacher-scholar model. All applicants must be work-eligible. Applications due by November 3, 2006. For full announcement, including application instructions, see **website: http://www.iup.edu/biology** or **website: http://www.iup.edu.humresources/jobline** or call **telephone: 724-357-2352.** *Indiana University of Pennsylvania is an Equal Opportunity Employer (Minorities/Females/Persons with Disabilities/Veterans) and is a member of the State System of Higher Education.*

TENURE-TRACK FACULTY Microbiology

Washburn University's Biology Department invites applications for a tenure-track microbiology position beginning August 2007. Qualifications: Ph.D. in microbiology or related field. Commitment to quality undergraduate education. Preference given to candidates with demonstrated teaching excellence. Responsibilities: Teach majors'/pre-nursing classes in microbiology and upper-division courses in candidate's area of expertise; supervise undergraduate research. Rank: **ASSISTANT PROFESSOR.** Pending funding, candidates with Ph.D. and established teaching/research record at university level will be considered for **ASSOCIATE PROFESSOR** rank. Minimum salary: $42,000. Application review begins December 1, 2006, and continues until suitable candidate is identified. Send curriculum vitae, statements of teaching/research philosophies, transcripts, three reference letters to: **Dr. Susan Bjerke, Biology Department, Washburn University, Topeka, KS 66621. Website: http://www.washburn.edu.** *Washburn University is an Equal Opportunity Employer.*

POSITIONS OPEN

The Department of Chemistry and Biochemistry at the University of Oklahoma invites applications for a tenure-track faculty position in analytical chemistry at the rank of **ASSISTANT or ASSOCIATE PROFESSOR.** Applicants must have the Ph.D. degree in chemistry, biochemistry, or closely related area. For an appointment at the rank of Assistant Professor, the candidate must have postdoctoral or related experience. We are seeking individuals with a strong interest in teaching both at the undergraduate and graduate levels in the area of analytical/bioanalytical chemistry. We are especially interested in candidates who will contribute to a University-wide Integrative Life Sciences Research Initiative. Research areas of high interest include bioanalytical chemistry, particularly relating to neurochemistry/neuroscience, mass spectrometry-based proteomics, metabolomics, and related biological applications of mass spectrometry, and the development of sensors for biomedical, environmental, and security applications. Applicants for a senior faculty position must have a proven record of sustained and substantial external research grant funding. Interested individuals should submit curriculum vitae, a detailed description of their research plans, and a statement of teaching interests and philosophy. Candidates for Assistant Professor should request three letters of recommendation and have them sent directly to the **Chair of the Search Committee;** candidates for Associate Professor should identify three individuals whom the Search Committee may contact for letters of recommendation. Send application materials to: **Professor Glenn Dryhurst, Chair of Analytical Faculty Search Committee, Department of Chemistry and Biochemistry, 620 Parrington Oval, Norman, OK 73019.** We will also accept completed applications in PDF format sent to **e-mail: sgfisher@ou.edu.** The review of applications will begin on November 15, 2006, and will continue until the position is filled. *Minorities and women are especially encouraged to apply. The University of Oklahoma is responsive to the needs of dual-career and is an Affirmative Action Equal Opportunity Employer.*

ASSISTANT/ASSOCIATE PROFESSOR, PHARMACOLOGY. The Department of Biomedical Sciences (BMS) seeks to fill an Assistant/Associate Professor tenure-track position in the area of pharmacology. The successful applicant is expected to develop an independent, extramurally funded research program, contribute to professional veterinary pharmacology teaching, and contribute to graduate and undergraduate educational programs. There is a potential to interface with research faculty in the areas of neuroscience, cardiovascular, or reproductive biology. Applicants with a pain, cardiovascular, or autonomic research focus are particularly encouraged to apply. Information about the position and the BMS Department can be found at **website: http://www.cvmbs.colostate.edu/bms.** Applicants must hold a Ph.D., D.V.M., M.D., or equivalent degree and have a minimum of two years of postdoctoral experience. Send cover letter, curriculum vitae, list of three references, description of research program, statement of teaching interests, and copies of three most important publications to **e-mail: douglas.ishii@colostate.edu,** or **Dr. Douglas Ishii, Department of Biomedical Sciences, Campus Delivery 1680, Colorado State University, Fort Collins, CO 80523-1680.** Review of applications will begin November 10, 2006, and continue until the position is filled. *Colorado State University is an Equal Opportunity/Affirmative Action Employer.*

ASSISTANT PROFESSOR Utah State University

The Department of Wildland Resources is seeking an **ANIMAL POPULATION ECOLOGIST** studying the structure and dynamics of populations in terrestrial systems to fill an Assistant Professor position in animal population ecology. An earned Ph.D. in animal ecology or a related discipline is required. See **website: http://jobs.usu.edu** (requisition identification 050526) for full job description and to apply online. *Affirmative Action/Equal Opportunity Employer.*

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Faculty of Science, School of Biological and Chemical Sciences

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Professor David Latchman, Master.

Applications are invited for a Chair in Chemical Biology to be held in the School of Biological and Chemical Sciences at Birkbeck. We are looking for an outstanding individual in the field of chemical biology, with a strong track record of external fundraising and an international level research programme.

The Chair of Chemical Biology at Birkbeck will be expected to lead the development and implementation of the College's research strategy and to have a central role in the development of chemical biology research in the Bloomsbury area, working in conjunction with the ISMB and the Centre for Chemical Biology at UCL. The potential also exists for research collaborations with the School of Pharmacy.

The successful applicant will be expected to play a key role in developing the future research strategy of the School of Biological and Chemical Sciences, and will also be expected to oversee the design and development of the curriculum in chemical biology in order to ensure teaching within the quality assurance framework of the College.

The salary is negotiable and is anticipated to reflect the high calibre of the successful applicant.

Download the job description and application form by visiting www.bbk.ac.uk/hr/vacancies or email humanresources@bbk.ac.uk for an application pack.

Closing date for applications is Friday 17th November 2006.

Birkbeck is an equal opportunities employer

TENURE-TRACK
ASSISTANT PROFESSOR
Chemical Biology/Medicinal Chemistry

The South Carolina College of Pharmacy Department of Pharmaceutical Sciences is seeking highly qualified applicants for a faculty position at the **ASSISTANT PROFESSOR** level. The position will be located on the Medical University of South Carolina (MUSC) campus in Charleston with a joint appointment at the University of South Carolina (USC), Columbia. MUSC and USC have made strong commitments to building a nationally recognized Drug Discovery Program, including the recruitment of several senior faculty members and construction of a new building to house the Program. State-of-the-art research facilities, including x-ray crystallography, NMR and mass spectrometry, molecular modeling, proteomics and lipidomics are available to support the Program. Preferred qualifications for this new faculty position include demonstrated experience in the use of chemical approaches in drug development, particularly for cancer. The successful candidate will be responsible for developing an extramurally funded research program, and participating in Departmental teaching. Excellent opportunities for collaborations within MUSC and the USC, and generous start-up funds are available.

Interested candidates should submit their curriculum vitae, statement of research interests, and the names of three references to: **Charles D. Smith, Ph.D., Department of Pharmaceutical Sciences, Medical University of South Carolina, 280 Calhoun St., PO Box 250140, Charleston, SC 29425** or by email to: **smithchd@musc.edu**. *MUSC is an Affirmative Action/Equal Opportunity Employer.*

TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER
School *of* Medicine™

FACULTY POSITIONS IN VIROLOGY AND IMMUNOLOGY
ASSISTANT, ASSOCIATE, AND FULL PROFESSOR TENURE TRACK POSITIONS

The Department of Microbiology and Immunology is seeking candidates for multiple faculty positions at the level of **ASSISTANT, ASSOCIATE**, and **FULL PROFESSOR**. The department is especially interested in candidates with research interests in the biology or pathogenesis of animal or human viruses and in the area of immunology. Specific areas of research interest could include: **AIDS AND HEPATITIS VIRUSES, CANCER, AND EMERGING INFECTIOUS DISEASES**. Groups of investigators with programmatic themes are encouraged to apply. Individuals with a Ph.D., M.D., and/or D.V.M. degrees, postdoctoral experience, and a strong record of research accomplishments will be considered. Applicants at the Associate and Full Professor levels are expected to have an established extramurally funded research program. New faculty will be expected to establish vigorous research programs supported by extramural sources. All faculty participate in the teaching of medical and graduate students. The department is beginning a major faculty expansion that includes new laboratories and major equipment acquisition. Substantial start-up funds will be available to new faculty. The Health Sciences Center is part of the Texas Tech University System, the only university system in the state with a comprehensive general academic university, law school and Health Sciences Center on the same campus. Texas Tech University is the largest university in West Texas, and is a Carnegie I institution providing education to approximately 25,000 students. This represents a unique opportunity to live in a college campus environment where the cost of living is affordable and opportunities abound.

To apply, please fill out an application at **http://jobs.texastech.edu**; using requisition number **61541** for **assistant**, requisition number **61546** for **associate**, and requisition number **61639** for **full professor** positions. Include your curriculum vitae and a description of research accomplishments. Please arrange for at least three individuals to provide letters of reference which should be sent to: **Dr. Ronald C. Kennedy, Professor and Chair, Department of Microbiology and Immunology, Texas Tech University Health Sciences Center, 3601 4th Street STOP 6591, Lubbock, Texas 79430-6591**. Inquiries about the position can be sent to **MicroandImmuno@ttuhsc.edu**.

TTUHSC is an EEO/AA/ADA Employer.

POSITIONS OPEN

ASSISTANT PROFESSOR
Department of Pharmaceutical Sciences
Tenure Track, Begin July 1, 2007

The Philadelphia College of Pharmacy, the foundational College of the University of the Sciences in Philadelphia, invites applications for a new tenure-track faculty position at the rank of Assistant Professor in the Department of Pharmaceutical Sciences, to begin on or about July 1, 2007. The candidate must have a Ph.D. degree in an area relevant to pharmaceutical sciences. The successful candidate should have strong research interests that complement existing areas within the Department and demonstrate a record or potential of obtaining extramural funding. The successful candidate will participate in the teaching of pharmacology at undergraduate, professional (Pharm.D.), and graduate levels.

The Department consists of 13 tenure-track and two nontenure-track faculty, three Postdoctoral Fellows, five staff members, and approximately 165 undergraduate majors in the B.S. Programs in Pharmacology/Toxicology and Pharmaceutical Sciences, as well as approximately 55 students in the graduate programs. The Department has a state-of-the-art, Association for Assessment and Accreditation of Laboratory Animal Care-accredited, fully staffed vivarium, tissue culture facilities, and a wide array of analytical instruments including high performance liquid chromatography, liquid chromatography/mass spectrometry, flow cytometer, absorbance and fluorescent plate readers, image analyzers, and scanning electron microscope. In addition, the Department has a fully equipped manufacturing/industrial pharmacy laboratory that is used for teaching and academic/contract research. The new McNeil Science and Technology Center, completed in August 2006, provides increased space for research and/or teaching in line with the University's strategic imperative to increase research activities. There is also a variety of research equipment such as fluorescence spectrophotometer, infrared spectrometer, nuclear magnetic resonance, and confocal microscope, housed in the Departments of Chemistry and Biology and are available for faculty research.

Interested parties are encouraged to consult our **website: http://www.usip.edu** for additional information. Each candidate should submit curriculum vitae, letter of application that addresses research interests and teaching experience, and contact information for at least three references as soon as possible to: **Ruy Tchao, Ph.D., Chair, Faculty Search Committee, University of the Sciences in Philadelphia, 600 S. 43rd Street, Philadelphia, PA 19104. E-mail: r.tchao@usip.edu, telephone: 215-596-8978.** Application review will begin immediately; applications will be accepted until the position is filled.

Equal Opportunity/Affirmative Action Employer.

SCIENCE PEDAGOGIST
Bucknell University

The Biology Department at Bucknell University invites applications for a tenure-track **ASSISTANT/ASSOCIATE PROFESSOR** to begin August 2007. We are seeking a broadly trained Biologist with a specialty in science pedagogy who will teach nonmajor courses and participate in the development of new science curricular initiatives. The successful candidate is expected to establish a research program in college science pedagogy that involves talented undergraduates and attracts extramural funding. Ph.D., postdoctoral experience, evidence of teaching effectiveness, and a strong research record are required. Bucknell University is a premier liberal arts University with a long-standing tradition of excellence in the sciences. Startup funds and internal funding for research are available. To apply, please refer to **website: http://www.bucknell.edu/jobs.** Review of applications will begin on November 3, 2006. The search will remain open until the position is filled.

An Equal Opportunity/Affirmative Action Employer, Bucknell University especially welcomes applications from women and minority candidates.

POSITIONS OPEN

RESEARCH INITIATIVE IN PHOTOCHEMICAL SCIENCES/ BIOSCIENCES

The Center for Photochemical Sciences and the Departments of Biological Sciences and Chemistry at Bowling Green State University wish to expand their Research Initiative, interfacing biology, chemistry, and photochemical sciences. Applications are invited for one **ASSISTANT PROFESSOR** tenure-track appointment. The successful candidate will develop and apply photochemical, biophysical, and molecular biology approaches to study the structure, function, dynamics, and interactions of biomolecules and cellular events. Such techniques can include, but are not restricted to, single molecule methods or imaging techniques.

The Department of Chemistry provides a stimulating research environment conducive to faculty success (see **website: http://www.bgsu.edu/departments/chem/).** Its facilities include the Ohio Laboratory for Kinetic Spectrometry which maintains modern transient spectrometry facilities operating within the femtosecond and longer time domains, and the Wright Photosciences Laboratory which provides unique opportunities for interactions with Industrial Photoscientists. **Dr. H. Peter Lu,** the newly-appointed Ohio Eminent Scholar in the Photochemical Sciences, is establishing a laboratory for single molecule spectrometry, and **Dr. Massimo Olivucci,** a senior appointee, is initiating a laboratory for computational photochemistry.

The appointment will be made within the Department of Biological Sciences, a Ph.D.-granting Department having active research programs in diverse areas of biology (see **website: http://www.bgsu.edu/departments/biology/).** The successful candidate will have a demonstrated record of productivity in the above-mentioned areas and will be expected to develop strong, extramurally funded research programs in their research specialization. Interested candidates should send a copy of their curriculum vitae, statements of research and teaching interests, representative publications, and three letters of recommendation to the address below.

Applications should be sent to: **Professor Michael A. J. Rodgers, Ohio Eminent Scholar and Chair, Research Initiative Search Committee, c/o The Department of Biological Sciences, Bowling Green State University, Bowling Green, OH 43403.** Review of applications will begin November 15, 2006, and will continue until the position is filled. *Bowling Green State University is an Affirmative Action/Equal Employment Employer and encourages applications from women, minorities, veterans, and individuals with disabilities.*

TWO FACULTY POSITIONS IN THEORETICAL CHEMISTRY
University of California, Irvine

The Department of Chemistry at the University of California, Irvine (UCI), seeks to continue building on its existing breadth and strength in theoretical chemistry by making two new faculty appointments. Applications are invited from both **JUNIOR and SENIOR RANKS** in all areas of theoretical and computational chemistry, including, for example, methods development and application in the traditional areas of electronic structure, statistical mechanics, and dynamics, as well as interdisciplinary areas interfacing with biophysics, chemical biology, chemical engineering, materials science, chemical physics, nanotechnology, and bioinformatics. Candidates should have a visionary research program, and commitments to teaching and to the creation of a center of excellence in theoretical chemistry at UCI. A Ph. D. degree is required. To apply, electronically submit curriculum vitae, statements of research and teaching interests, and at least three letters of recommendation. Application instructions may be found at **website: http://ps.uci.edu/employment/apply.html.** Review of applications will begin November 15, 2006. *The University of California, Irvine, is an Equal Opportunity/Affirmative Action Employer committed to excellence through diversity. UC Irvine has an active Career Partners Program and has an ADVANCE Gender Equity Program.*

POSITIONS OPEN

FACULTY POSITION
University of Minnesota
Department of Genetics, Cell Biology, and Development

The Department of Genetics, Cell Biology, and Development (GCD) is conducting a search for faculty, at any level, working in the general area of mobile DNA, including transposable elements, chromosome rearrangement, gene therapy, and insertional mutagenesis. The Department will devote a competitive salary, startup package, and modern laboratory space, with access to state-of-the-art core facilities in genomics/proteomics, transgenics, stem cell technology, tissue procurement, flow cytometry, statistics, analytical chemistry, and cell therapy. The candidate must have a Ph.D. or M.D., at least three years of postdoctoral experience, with evidence of high quality research productivity. Emphasis will be placed on the potential for interaction with existing research programs in GCD, particularly the members of the Arnold and Mabel Beckman Center for Transposon Research **(website: http://beckmancenter.ahc.umn.edu/).** The person selected will be expected to develop an independent, funded research program and participate in the teaching mission of the Department.

Individuals interested in this position should apply online **(website: https://employment.umn.edu).** Search for requisition number 143261. Attach curriculum vitae and a brief statement of current and future research. Three letters of reference should be mailed to: **GCD Mobile DNA Faculty Search, c/o Mary Muwahid, University of Minnesota, Department of Genetics, Cell Biology and Development, 6-160 Jackson Hall, 321 Church Street S.E., Minneapolis, MN 55455 (e-mail: muwah001@umn.edu).**

Applications will be accepted until the position is filled.

The University of Minnesota is an Equal Opportunity Educator and Employer.

COASTAL RESEARCH FACULTY POSITIONS

The Louisiana Universities Marine Consortium (LUMCON, **website: http://www.lumcon.edu)** invites applications for three **ASSISTANT PROFESSORS.** Research opportunities include extensive marsh, estuarine, and coastal ocean ecosystems, the Mississippi River/Gulf of Mexico system, and a seawater system and racetrack flume. Expertise preferred in phytoplankton ecology, wetlands ecology and restoration, and biogeochemistry. The positions carry nine months of salary support; initial appointment for three years within a multi-year renewable contract. Submit electronic copies of a letter of interest, curriculum vitae, statement of research and education interests, and the name, affiliation, address, telephone, and e-mail address of three references to: **Dr. Nancy N. Rabalais, Executive Director, e-mail: nrabalais@lumcon.edu (telephone: 985-851-2801).** Review of applicants will begin December 1, 2006. *LUMCON is an Affirmative Action/Equal Opportunity Employer.*

RESEARCH ASSOCIATE (ASSISTANT PROFESSOR) POSITIONS available in the Department of Neurology to study the molecular and cellular pathogenesis *spinocerebellar ataxias* and other neurodegenerative disorders. Candidates must have a doctorate in biological sciences, molecular biology, or a related field with at least four years of experience in experimental neuroscience. Salary will be commensurate with background and experience. Send curriculum vitae, a personal research statement, names of three references, and up to five best publications to **Dr. Christopher M. Gomez** as hard copy: **Department of Neurology, MC2030; University of Chicago; 5841 South Maryland Avenue; Chicago, IL 60637 (fax: 773-702-5670)** or via **e-mail: cgomez@neurology.bsd.uchicago.edu** with Microsoft Word and PDF files as needed. Screening of applications will continue until the position is filled. *The University of Chicago is an Affirmative Action/Equal Opportunity Employer.*

MAX-PLANCK-GESELLSCHAFT

The Max Planck Institute of Biophysics in Frankfurt am Main invites applications for the position of an

Independent Junior Research Group Leader

The group will be established in association with the Physics Department of the Goethe University, Frankfurt am Main.

Applicants should have a strong research record in theoretical biophysics in an area that complements the research interests of the three existing departments at the Max Planck Institute **(http://www.mpibp-frankfurt.mpg.de/)**. Computational approaches to membrane protein structure and function are of particular interest.

The position is funded for 5 years, with the possibility of extension at a more advanced level. The new research group leader is expected to participate in the new biophysics curriculum **(http://www.physik.uni-frankfurt.de/)** at the University and will have the opportunity to join the DFG-funded areas of special study (Sonderforschungsbereiche) in Frankfurt.

The University of Frankfurt and the Max Planck Society are equal opportunity employers, and particularly encourage female applicants, to increase the share of women in areas where they are under-represented. Both institutions also try to increase the proportion of scientists with physical disabilities. Respective applications are particularly welcome.

Applications with the usual information (curriculum vitae, list of publications, reprints or electronic copies of the 5 most important papers, details of teaching experience, a short statement of research interests and three references) should be sent to:

Max-Planck-Institut für Biophysik
Geschäftsführender Direktor
Max-von-Laue-Str. 3
D-60438 Frankfurt am Main, Germany

Deadline for application is **November 10th, 2006**.

JOHANN WOLFGANG GOETHE
UNIVERSITÄT
FRANKFURT AM MAIN

The Physics Department of the Johann Wolfgang Goethe-Universität Frankfurt am Main invites applications to fill a position for an independent research group leader in

Experimental Biophysics as Associate Professor (W2)

The Institute for Biophysics offers a stimulating atmosphere with a unique infrastructure in the fields of molecular spectroscopy and time-resolved spectroscopy (http://atlas.biophys.uni-frankfurt.de/). Possible areas of research for the applicant are optical spectroscopy at high spatial resolution or beyond diffraction limits, including methods development. Teaching involves biophysics courses for physics, chemistry and biology students as well as in the newly developed Bachelor/Master courses in Biophysics. In addition, contributions to physics courses for students at medical school are expected. The position is limited for 5 years. Frankfurt University is committed to equal opportunities and selection on merit.
The position is subject to the requirements laid down in paragraphs §70(6) and §71 of the Hessisches Hochschulgesetz. Successful candidates will be required to participate in the self-government of the University. The Johann Wolfgang Goethe-Universität is attempting to increase the proportion of women among its scientific personnel; women are therefore especially urged to apply. In 2005, Frankfurt University was awarded the certificate "Familiengerechte Hochschule". Employees will be supported in their efforts to combine their professional life with family duties. Candidates, coming back to work after maternity/paternity leave, are encouraged to apply for reemployment. Precedence is given to handicapped persons at equal qualification.

Applications, accompanied with the usual information (curriculum vitae, list of publications, reprints or electronic copies of the five most relevant papers, details on teaching experience and a short summary of research interests), should be sent to: **Dekan des Fachbereichs Physik der Johann Wolfgang Goethe-Universität, Prof. Dr. W. Aßmus, Max-von-Laue-Straße 1, D-60438 Frankfurt am Main, http://www.unifrankfurt.de/fb/fb13/index.html**

Applications are requested before **10th November 2006.**

www.uni-frankfurt.de

Hier wird Wissen Wirklichkeit

UNIVERSITÄT BASEL

The Medical Faculty of the University of Basel, Switzerland invites application for the position of

a full Professor in Pharmacology (Ordinariat)

at the Biozentrum. We seek an outstanding individual whose research efforts should integrate and complete the present research areas of pharmacological research in the field of human pharmacology (pharmacogenomics, signal transduction pathways, systems pharmacology). Start up funds as well as substantial funding for post doctoral fellows, technical staff and running costs are available. The candidate's research group will be housed in a generous space at the Biozentrum and provided with state of the art facilities and infrastructure. Ample opportunity is available for interaction established in the Biozentrum or Pharmazentrum as well as with many other University Hospital and industry research groups nearby. In addition interaction will also be possible with the newly created Institute for System Biology established in Basel (ETHZ in Basel). The successful candidate will develop a highly competitive research program and participate in the teaching of pharmacology for medical and science students.

Individuals with an established research record are invited to apply. Applications from women are particularly welcome.

Applications should include a curriculum vitae, a list of publications, a brief summary of present and future research interests and the name of three references. Documents should be sent to:

Prof. Jürg Schifferli, Vorsitzender Kommission Pharmakologie, Vorsteher Departement Innere Medizin, Universitätsspital, Petersgaben 4, CH-4031 Basel, by November 30, 2006.

Informal inquiries can be addressed to Prof. Joachim Seelig, Biozentrum,
e-mail: Joachim.seelig@unibas.ch, or to Prof. Jürg Schifferli, Universitätsspital,
e-mail: j.schifferli@unibas.ch.

UNI
BASEL

ASSISTANT/ASSOCIATE/FULL PROFESSOR
(Molecular Pathogenesis/Tenure-Track or Tenured/One or more positions)
School of Veterinary Medicine/Pathobiological Sciences (PBS)

The Department of Pathobiological Sciences (PBS) at the Louisiana State University (LSU) School of Veterinary Medicine has embarked on a second phase of its strategic growth plan that has created one or more additional tenure-track or tenured faculty positions at the levels of Assistant, Associate, or Full Professor. Applications are sought from candidates with research interests that strengthen or complement the Department's current programs in infectious diseases. The PBS Department has close ties with the LSU Agricultural Center, the National Hansen's Disease Center, the Tulane National Primate Research Center and LSU Medical Center in New Orleans. The School of Veterinary Medicine is an active participant in Louisiana State University's Information Technology and Biotechnology initiatives. The Department houses modern research laboratories enhanced by centralized PCR and microarray analyses, laser capture microdissection, fluorescence and electron microscopy, laser confocal microscopy, flow cytometry, proteomics, in vivo imaging, and BSL-3 laboratory suites. More information on the Department is available at **http://www.vetmed.lsu.edu/pbs/**.

Required Qualifications: (**All levels**) D.V.M., M.D., and/or Ph.D. in an area related to disease pathogenesis at the cellular and/or the molecular level; post-doctoral training related to molecular pathogenesis; (**Associate or Full Professor**) history of independent funding. Additional **Qualifications Desired:** (**All levels**) working in the areas of immunological and molecular mechanisms of pathogenesis for intracellular parasites, bacterial, and viral pathogens. **Responsibilities:** (**All levels**) establishes outstanding independent research programs that will attract continued extramural funding; participates in the teaching mission of the Department.

As part of the Department's emphasis on the growth of its research program, highly competitive salary and start-up packages are available. Appointments will be at the Assistant, Associate, or Full Professor levels, depending on experience. An offer of employment is contingent on a satisfactory pre-employment background check. Review of the applications will begin on **November 15, 2006**, and will continue until candidates are selected. Inquiries should be directed to **Dr. Konstantin G. Kousoulas, Chair of the Faculty Search Committee, Phone (225)578-9683**, or E-mail: **vtgusk@lsu.edu**. Interested candidates should submit an electronic copy of the following: a curriculum vitae (including e-mail address), a statement of research interests along with future research goals, and the names, postal and e-mail addresses, and phone numbers of at least three referees to: **Tracy Rook, Department of Pathobiological Sciences, School of Veterinary Medicine, Louisiana State University, Ref: Log #0751, Baton Rouge, LA 70803; Phone: 225-578-9684; E-mail: trook@vetmed.lsu.edu.**

LSU IS AN EQUAL OPPORTUNITY/EQUAL ACCESS EMPLOYER.

THE UNIVERSITY of TULSA

Assistant Professor
Plant Viral Biodiversity

The Department of Biological Science at The University of Tulsa seeks to appoint a tenure-track assistant professor with interests in plant virology. We seek a broadly trained biologist with interests in plant viral biodiversity who can interact with other departmental faculty studying virus ecology, immunology and molecular evolution. This position is part of a state-wide initiative to study plant viral biodiversity. Teaching interests should include molecular biology and genetics. The position begins no later than 15 August 2007.

Assistant Professor
Immunologist/Microbiologist

The Department of Biological Science at The University of Tulsa seeks to appoint a tenure-track assistant professor with interests in immunology. We seek a broadly trained biologist with interests in microbial/viral pathogenesis who can interact with other departmental faculty studying virus ecology and immunology. Teaching interests should include microbiology and immunology. The position begins 15 August 2007.

Assistant Professor
Animal Virology

The Department of Biological Science at The University of Tulsa seeks to appoint a tenure-track assistant professor with interests in animal virology. We seek a broadly trained biologist with interests in emerging infectious diseases who can interact with other departmental faculty studying virus ecology and molecular evolution. Teaching interests should include microbiology and virology. The position begins 15 August 2007.

The University of Tulsa is a private, comprehensive university with a strong commitment to research and teaching. The Department of Biological Science has a faculty of fourteen and offers BS, MS., and Ph.D. degrees. Applicants to these positions should have a Ph.D. degree and postdoctoral experience.

To apply to any of these positions, send curriculum vitae, statement of research and teaching interests, reprints, and three letters of reference to: **Search Committee Chair, Department of Biological Science, The University of Tulsa, 600 South College Avenue, Tulsa, Oklahoma 74104**. Indicate in your cover letter which position is of interest to you. Review of applications will begin immediately for the Plant Viral Biodiversity position and **November 1, 2006** for the Immunologist/Microbiologist and Animal Virology positions.

The University of Tulsa is an Equal Opportunity/Affirmative Action Employer.

UF UNIVERSITY of FLORIDA
The Foundation for The Gator Nation

DIRECTOR
UNIVERSITY OF FLORIDA
EMERGING PATHOGENS INSTITUTE

EPI Emerging Pathogens Initiative

The University of Florida seeks a Director for the University of Florida Emerging Pathogens Institute (EPI, **http://epi.ufl.edu**). The University of Florida has initiated establishment of the EPI, and the state of Florida has committed considerable resources to the EPI including funding for new faculty and a new research facility of approximately 100,000 sq. ft. The EPI is focused on relevant scientific, clinical, agricultural, social, and educational issues related to emerging diseases. This unique institute will develop and deliver appropriate informatics, diagnostics, treatments and surveillance for the prediction, prevention, detection and management of microbial pathogen-associated diseases of humans, animals and plants. The EPI will foster research into fundamental mechanisms of emerging pathogens; train scientists with integrated knowledge into the dynamics between human, animal and plant pathogens; integrate bioengineering and nanoscience technologies with pathogenesis research; expand research capabilities for development of vaccines and antimicrobial reagents; collaborate with state agencies in developing response and prevention plans; foster translational research in community settings, and coordinate implementation with relevant authorities.

The Director of the EPI will report to the Vice President for Research and will be responsible for facilitating the University-wide strategic research initiatives as well as the educational goals of EPI through resource acquisition (grant acquisition and fund-raising), as well as new faculty recruitment and facility development. The Director will also be responsible for the coordination, design, performance, and evaluation of new and existing educational programs within the Institute. Finally, the Director will be responsible for coordinating activities of all EPI faculty with appointments in the Colleges affiliated with the Institute.

The University of Florida, a public land-grant institution, is a member of the Association of American Universities (AAU), and one of the five largest universities in the nation with 38,000 undergraduate students and 10,000 graduate students. UF faculty attracted a record $494 million in research and training grants in 2003-04, placing the university among the nation's leading research institutions. UF is among the nation's most academically diverse universities, with 16 colleges offering 100 undergraduate degree programs, 200 graduate programs and 30 combined degree programs. UF is a perennial national leader in attracting National Merit and National Achievement Scholars and in the number of patents awarded to faculty researchers.

Candidates should have a Ph.D., M.D., D.V.M., D.D.S., or equivalent degree with a nationally recognized record of research achievement in the area of host-pathogen interactions and/or epidemiology, plus administrative experience. The academic appointment of the Director will be in the appropriate College, based on the candidate's qualifications and expertise. The position is available and the search will be continued until the position is filled. Compensation will be commensurate with qualifications and responsibilities. Qualified applicants should submit a curriculum vitae, a statement of interest, and the names and contact information of three referees to: **Elizabeth Shenkman, PhD, Chair EPI Search Committee, 1329 SW 16th Street, Room 5130, Gainesville, Florida 32608**. Because the University is committed to building an intellectual and culturally diverse educational environment, applicants should included in their cover letter information about how they will further this mission. Review of applications will begin on **October 23, 2006**.

Tenure-track **Assistant, Associate**, or **Full Professor** in **BIOMEDICAL SCIENCES**. Candidates are expected to contribute to cell biology or combined histology-physiology courses offered to professional and graduate students; conduct federally funded independent research programs; and to develop intellectual property that will contribute to the economic growth of Iowa. For this position there is an emphasis on an entrepreneurial activity, intellectual property, and contribution to economic growth, which is a developing area of interest in the department as well as the university. The Biomedical Sciences Department has research interests in cellular and molecular biology, neuroscience and neurotoxicology. An interest in one of these areas is encouraged, but applicants with interests in other fields may apply. The department is looking for an energetic candidate to join its expanding BMS faculty and who will advance its successful research, professional, and graduate programs along with interest in economic growth.

To guarantee consideration, applications must be received and submitted electronically by **December 31, 2006**. To apply, visit **www.iastatejobs.com** (Vacancy **#060725**) and complete the employment application form. Be prepared to attach a letter of application, curriculum vitae, teaching and research goals statement, and contact information for three references. Attach teaching and research goals statement as "other document". Direct inquiries regarding position to **James R. Bloedel**, Search Committee Chair **jbloedel@iastate.edu**, **515-294-4415**. For further information contact: **http://www.vm.iastate.edu/departments/bms**.

Iowa State University is an Affirmative Action/ Equal Opportunity Employer.

WASHINGTON STATE UNIVERSITY
FACULTY POSITIONS IN
MOLECULAR BIOSCIENCES/BIOCHEMISTRY AND MICROBIOLOGY

Two tenure-track faculty positions at the Assistant, Associate, or Full Professor level are available in the School of Molecular Biosciences (**http://molecular.biosciences.wsu.edu**) beginning August 16, 2007. We are seeking to hire one individual with training in biochemistry whose research focuses on enzymology, spectroscopy, or the structure and function of proteins, nucleic acids and membranes, and a second individual with training in infectious diseases whose research focuses on microbial pathogenesis, molecular microbiology, cellular microbiology, or microbial genomics. Candidates with expertise in computational/bioinformatics approaches are encouraged to apply. Candidates must have a Ph.D. in a discipline related to molecular biosciences, postdoctoral training, a record indicating outstanding potential in research, an interest in high quality undergraduate and graduate education, and the ability to communicate effectively with students and colleagues. Successful candidates will be expected to develop and maintain a vigorous research program supported by extramural funding, train graduate students, and participate in graduate and undergraduate teaching. Candidates applying for Associate and Full Professor level must have a strong publication record, extramural funding, and excellent teaching credentials.

Please submit your application, curriculum vitae, a detailed statement of research interests and goals via email to Kathy Pinter at **smbsearch@wsu.edu**. In addition, please have three letters of reference addressing outstanding abilities and potential in research and teaching sent to: **Dr. Michael Konkel, Search Committee Chair, School of Molecular Biosciences, Washington State University, Pullman, WA 99164-4234**. Screening of applications will begin **November 15, 2006**. Salary will be negotiable and commensurate with experience and qualifications. The Pullman campus, which serves approximately 18,600 students, is located in the rich agricultural area known as the Palouse in eastern Washington. The region offers many recreational activities including mountain biking, rock climbing, skiing, fishing, hunting, whitewater rafting, camping, and hiking.

WSU employs only U.S. citizens and lawfully authorized non-U.S. citizens.
WSU is an *Equal Opportunity/Affirmative Action Educator and Employer. Members of ethnic minorities, women, Vietnam-era or disabled veterans, persons of disability, and/or persons age 40 or over are encouraged to apply.*

Faculty Positions in Bioinformatics/Computational Biology
Center for Bioinformatics, The University of Kansas

The Center for Bioinformatics at The University of Kansas invites applications for two tenure-track faculty positions to begin as early as August 2007. The Center is a new initiative created as part of a major expansion in Life Sciences and complements existing strengths, including structural biology, computational chemistry, proteomics, drug design, developmental/molecular genetics, and information technology. The Center fosters international activities in Bioinformatics and combines outstanding research and an affiliated Ph.D. program. Center information: **www.bioinformatics.ku.edu**. We intend to make the faculty appointments this year jointly in the Center and in the Department of Molecular Biosciences (**www.molecularbiosciences.ku.edu**). Appointments are expected to be at the assistant professor level. **Duties:** to establish and maintain an externally funded research program, to participate in teaching, and to provide service. **Required Qualifications:** Ph.D. in a discipline related to Bioinformatics, postdoctoral experience; potential for excellence in research in Bioinformatics as evidenced by publications in highly ranked journals and innovation/productivity in research objectives; and commitment to teaching life sciences courses evidenced by teaching philosophy statement. The successful candidate for the position should be eligible to work in the U.S. prior to the starting date of the position. We seek candidates with research interests in the area of **modeling of protein interactions and computational proteomics**. The examples include but are not limited to:

- protein docking, binding site prediction, and binding simulations
- high-throughput modeling of protein structures
- modeling of protein networks and systems biology

For full position announcements, refer to: **www.clas.ku.edu**. Email CV, letter of application, statement of past and future research and teaching interests and philosophy, and a list of at least three referees to:

Dr. Ilya Vakser, Director and Professor
Center for Bioinformatics
The University of Kansas
2030 Becker Drive
Lawrence, KS 66047-1620

Direct inquiries to **Dr. Ilya Vakser** (**vakser@ku.edu**). Review of applications begins **November 1, 2006** and will continue until the positions are filled.

EO/AA Employer. Women, minorities, and candidates who will contribute to the climate of diversity in the College, including a diversity of scholarly approaches, are encouraged to apply.

TENURE TRACK POSITION
Department of Chemical Engineering and Materials Science
University of California-Davis

The Department of Chemical Engineering and Materials Science invites applications for a tenure-track position at the Assistant Professor level in the area of advanced (scanning) transmission electron microscopy ((S)TEM). In the last two years, UC-Davis has made a significant investment in electron microscopy facilities for both the engineering and biological sciences (including three new field-emission (S)TEMs). The current position seeks a candidate to work within this environment who has expertise in the development and application of advanced methods of imaging and analysis in (S)TEM for the engineering sciences, and who has a strong commitment to applying these methods to soft/biological materials. The successful applicant will be expected to develop an externally funded research program, assist in the routine operation and management of the microscopy facilities, and have a commitment to cross-disciplinary education at both the undergraduate and graduate level. Candidates are expected to have a PhD in materials science, physics, chemistry or related engineering discipline. Applicants should submit a letter of application, curriculum vitae (including list of publications), description of research and teaching plans, and names and contact information of at least three references at **http://www.chms.ucdavis.edu/employment/**. The position is open until filled; but to assure full consideration, online applications should be submitted no later than **November 30, 2006**, for a targeted start date of July 1, 2007. *The University of California is an Affirmative Action/Equal Opportunity Employer.*

UNIVERSITY OF CALIFORNIA, BERKELEY
SCHOOL OF PUBLIC HEALTH
DIVISION OF EPIDEMIOLOGY

A Faculty Position in Social Epidemiology

A faculty position in Social Epidemiology in the Division of Epidemiology of the School of Public Health at the University of California, Berkeley is available in the Fall, 2007. The School is particularly interested in candidates who have experience working with students from diverse backgrounds and a demonstrated commitment to improving access to higher education for disadvantaged students. Applications are invited for this new faculty position at the assistant professor level (tenure-track). Candidates should possess a research interest and expertise in the design, implementation, and interpretation of epidemiologic studies of how social and cultural factors influence human health and disease. The position offers an opportunity to collaborate with epidemiologists, biostatisticians, social and behavioral scientists, and faculty from other disciplines at the University of California, Berkeley (UCB), the University of California, San Francisco (UCSF), and other research organizations in the San Francisco Bay Area. Duties include developing and teaching upper division and graduate level courses in social epidemiology and epidemiologic methods, particularly methods that incorporate individual and group level variables, in addition to mentoring masters and doctoral degree students in this area. An MD, PhD, DrPH, or equivalent doctoral level degree in epidemiology, or a closely related discipline is required. Salary: Dependent upon individual qualifications.

Applications and related materials must be received by **December 15, 2006**. Send a letter of interest, curriculum vitae, list of publications, and four letters of recommendation to: **Arthur L. Reingold, MD, Chair, Search Committee, c/o Ronald Jeremicz, Division of Epidemiology, School of Public Health, University of California, Berkeley, 140 Warren Hall, MC# 7360, Berkeley, California 94720-7360.** Refer potential reviewers to the UC Berkeley Statement of Confidentiality found at: **http://apo.chance.berkeley.edu/evalltr.html**.

The University of California is an Equal Opportunity, Affirmative Action Employer.

Head, Department of Microbiology and Molecular Genetics
Oklahoma State University

The Department of Microbiology and Molecular Genetics at Oklahoma State University (OSU) invites applications for the position of Department Head. The position will carry the rank of Professor with tenure and will have a starting date on or after 1 August 2007. We seek a dynamic and visionary leader to help us increase our national prominence in our selected research areas: (1) Molecular Microbial Ecology, (2) Molecular Mechanisms of Pathogenesis, and (3) Molecular Microbial Physiology.

The ideal candidate will have a doctorate degree in Microbiology or a closely related field, a nationally recognized research program consistent with our research foci, demonstrated success in obtaining extramural grant support, significant administrative experience along with outstanding interpersonal and communication skills, a commitment to supporting innovative teaching, and a vision for curricular reform that will produce students highly qualified for careers in research, teaching, and other professional positions.

OSU is a land-grant institution with 24,000 students located in north-central Oklahoma, 70 miles from Oklahoma City and Tulsa. The Department of Microbiology and Molecular Genetics offers five options of B.S. degrees in Microbiology for undergraduate majors, and the M.S. and Ph.D. degrees in Microbiology for graduate students.

Qualified applicants should submit a letter of application, statements of research, teaching, and administrative philosophies, a curriculum vitae, and four letters of reference testifying to the applicant's leadership and administrative skills to: **Dr. James P. Wicksted, Chair, Department Head Search Committee, Department of Microbiology and Molecular Genetics, 307 LSE, Oklahoma State University, Stillwater, OK 74078-3020**. Telephone: **405/744-5796**; E-mail: **james.wicksted@okstate.edu**. Informal inquiries to **Dean Peter M. A. Sherwood** of the College of Arts and Sciences are welcome (Telephone: **405/744-5663**; email: **peter.sherwood@okstate.edu**). Application review will begin **1 January 2007** and will continue until the position is filled. For further information about the position, as well as descriptions of current research activities and educational programs please see the Departmental web site at **http://microbiology.okstate.edu**.

Oklahoma State University encourages applications from qualified women, minorities, and persons with disabilities.

UNIVERSITY OF CALIFORNIA
UC RIVERSIDE

College of Natural and Agricultural Sciences
Tenure-track Faculty Positions

The College of Natural and Agricultural Sciences at the University of California, Riverside is recognized for its outstanding programs in all of the core sciences and is active in campus-wide initiatives in the environmental sciences, genome biology, and materials science. The distinctive structure of the College – unifying the biological, physical, mathematical, and agricultural sciences under one organizational umbrella fosters cross-departmental collaboration and innovation. Located in the rapidly growing Inland Southern California region, UC Riverside is one of 10 campuses of the University of California, offering students a supportive, collegial learning environment. The College is seeking to appoint new faculty members in the following disciplines:

Algebra
Analysis
Bioinformatics and Computation Biology (3 positions)
Biol./Mgmt. of Prokaryotic Plant Pathogens
Computational Space Physics
Experimental Nanoscale Elec. Mat. and Device Physics (2 positions)
Geophysics
Insect/Plant Pathogen Interactions
Invertebrate Ecotoxicology
Mgmt. of Disease of Ornamental Crops
Molecular Biology of Insects
Org./Inorg./Biol. and/or Materials Chemistry
Plant Evolutionary Genomics
Pure Mathematics
Stem Cell Biology
Subtropical Plant Pathology
Synaptic Plasticity/Glial Neuronal
Theoretical/Computational Chemistry
Turfgrass Management

In addition to those listed, we anticipate that searches in Conservation Biology, Cosmology, Functional Landscape Ecology, and Insect Pests of Ornamentals will commence in the near future.

Visit www.cnas.ucr.edu/employment.html for information.

The University of California is an Equal Opportunity/Affirmative Action Employer.

Faculty Position in
Air Pollution Health Effects

The University of Texas School of Public Health

The Division of Environmental and Occupational Health Sciences at The University of Texas School of Public Health is seeking an experienced researcher in air pollution and its health effects with a strong track record of extramural funding to join our faculty as a tenure-track full professor. The successful candidate will be a nationally recognized expert in a topical area germane to air pollution and its health effects. The candidate will be expected to develop a robust extramurally-funded research program in this area and participate actively in defining future directions for research in the air environment. Additionally, s/he will contribute to the educational mission of the School and perform community service.

Qualifications include: (1) a doctoral degree in environmental health or a relevant field; (2) commitment to excellence in teaching and advising graduate students; (3) an established record of funded research; and (4) excellent written and oral communications skills.

Review of applications will begin immediately and continue until the position is filled. Candidates should send a letter describing their qualifications and interests along with their curriculum vitae and contact information for three professional references to: **Ken Sexton, Sc.D., Chair, Search Committee, Attention: Ms. Anne Dybala, The University of Texas School of Public Health, 1200 Herman Pressler, W-1020, Houston, TX 77030, email: Anne.L.Dybala@uth.tmc.edu**.

The University of Texas Health Science Center at Houston is an EO/AA employer. M/F/D/V. This is a security sensitive position and thereby subject to Texas Education Code §51.215. A background check will be required for the final candidate.

THE UNIVERSITY of TEXAS
HEALTH SCIENCE CENTER AT HOUSTON

DUKE NUS
GRADUATE MEDICAL SCHOOL SINGAPORE

Faculty Positions
– All Ranks –

Tenure-track faculty positions at all levels are available at the Duke-NUS Graduate Medical School Singapore (GMS). The GMS is unique in bringing post-baccalaureate, research-intensive medical education to Asia, and represents a truly global partnership between two leading U.S. and Asian universities. The GMS shares a modern campus with Singapore's largest hospital and several national research centers.

We are seeking creative individuals who are focusing on discovery biology and translational medicine in any thematic area, but with particular emphasis on (i) Cancer and Stem Cell Biology, (ii) Neurobehavioral, Cardiovascular, Metabolic and Ocular Disorders, or (iii) Infectious Diseases. Special opportunities and infrastructure exist for research involving advanced imaging of animals and humans, biorepositories and human cohort studies, and non-human primates. The pioneering faculty will join a number of Duke and Singapore investigators already affiliated with the GMS (see **www.gms.edu.sg**). Faculty positions include full salary, generous start-up, and five years of annual research funding of up to S$500K/p.a., assuring a stable base of support that can be supplemented by competitive grant awards, which are expanding rapidly in Singapore.

Interested candidates should send a CV, a statement of research interests, and arrange for three letters of reference to be sent (Assistant Professor candidates), or provide contact information for three references (Associate and Full Professor candidates), to: **Patrick J. Casey, Ph.D., Senior Vice Dean of Research, Duke-NUS Graduate Medical School Singapore, 2 Jalan Bukit Merah, Singapore 169547, or by email to: faculty.recruit@gms.edu.sg**

The GMS is a collaboration of the Duke University School of Medicine and the National University of Singapore.

FACULTY POSITIONS
in the
Department of Biological Sciences
Simon Fraser University

SIMON FRASER UNIVERSITY

The Department of Biological Sciences seeks to fill two tenure-track faculty positions, one in **microbiology** with a research focus on bacteria, fungi or parasites, and one in **molecular toxicology**, including nanotoxicology and toxicogenomics. We are especially interested in applicants whose research will complement existing strengths in the Department (**http://www.sfu.ca/biology**). Appointments will be made at the Assistant Professor level. Successful candidates will pursue vigorous, externally funded research programs that include the training of graduate students. They will be expected to contribute to the teaching of current core undergraduate courses, as well as developing graduate courses in their areas of expertise.

Review of applications will begin on **November 1, 2006** for the microbiology position and **November 15, 2006** for the toxicology position, and the search will remain active until the positions are filled. Applicants should send a curriculum vitae, three representative reprints, a one-page summary of their research objectives and teaching philosophy, and three letters of reference to: **Dr. Tony D. Williams, Chair, Department of Biological Sciences, Simon Fraser University, 8888 University Blvd., Burnaby, B.C. V5A 1S6, Canada; FAX: 604-291-4312.**

Simon Fraser University, located in the greater Vancouver area, is committed to employment equity, welcomes diversity in the workplace, and encourages applications from all qualified individuals including women, members of visible minorities, aboriginal persons, and persons with disabilities.

Under the authority of the University Act personal information that is required by the University for academic appointment competitions will be collected. For further details see: **http://www.sfu.ca/vpacademic/Faculty_Openings/Collection_Notice.html**.

All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. The appointment is subject to final budgetary approval by the University.

SYRACUSE UNIVERSITY
Department of Biology
Tenure-Track Faculty Position in Life Sciences Education

The Department of Biology at Syracuse University invites applications for a tenure-track position (Assistant or Associate Professor, depending on experience and qualifications) to begin in August 2007. Applicants must have a Ph.D. in a life sciences discipline and demonstrated experience with, and research interest in, undergraduate education. Preference will be given to those individuals having taught life sciences using active, inquiry-oriented instructional approaches and who have refereed publications in the domain of undergraduate life science pedagogy. Potential ability to attract extramural support for research focused on undergraduate teaching, curriculum and/or assessment issues in the life sciences will be an important consideration. The successful candidate will be responsible for the introductory biology teaching program at Syracuse University while maintaining an active life sciences education research program.

The successful applicant will benefit from the department's move into the new Life Sciences Building in 2008 with modern lecture, recitation and laboratory facilities (see **http://lifesciences.syr.edu/main.html** for details) and from collaboration opportunities with faculty in other Syracuse University science departments as well as in the Department of Science Teaching (see **http://scied.syr.edu**). Additional information about Biology at Syracuse University is available at: **http://biology.syr.edu/**.

Applicants should forward a cover letter, an up-to-date curriculum vitae, a description of her/his philosophy of teaching introductory biology to both biology and non-biology majors and a statement of proposed future education research goals. It is strongly preferred that application materials be sent as PDF attachments to the following email address: **Biosearch@cas.syr.edu**. The candidate should arrange to have at least three letters of reference sent directly to the address below. Please include in your application material the names, addresses, phone numbers and e-mail addresses of your references. The position will be open until filled, but we urge that you arrange to have all necessary materials to us by November 15, 2006.

Applications and reference letters should be addressed to: **Biology Educator Search, Department of Biology, 130 College Place, Syracuse University, Syracuse, NY 13244**.

Syracuse University has a strong commitment to equality of opportunity and a diverse workforce.

Syracuse University is an equal opportunity/affirmative action employer.

TENURE-TRACK FACULTY POSITION
Department of Surgery
The University of Chicago

The Department of Surgery at The University of Chicago seeks applicants for a faculty position at the rank of ASSISTANT or ASSOCIATE PROFESSOR with an interest in embryonic stem cells and formation of endoderm and endoderm-derived tissues. Prerequisite include an established record of independent investigation and peer-reviewed grant funding. Preference will be given to scientists (Ph.D. and/or M.D.) with research interests that complement and enhance ongoing research in islet and other cells of endodermal origin in the Departments of Surgery and Medicine.

Please send curriculum vitae, an outline of research plans, and the names of three references in electronic format (Word Document or PDF) to: **Dr. Michael Millis, Chief, Section of Transplantation Surgery, University of Chicago, Chicago IL, 5841 S. Maryland Ave., MC5027, Chicago IL 60637, e-mail: mmillis@surgery.bsd.uchicago.edu.**

THE UNIVERSITY OF CHICAGO

The University of Chicago is an Affirmative Action/Equal Opportunity Employer.

NORTHWESTERN UNIVERSITY

Neurobiology and Physiology
Tenure-track Faculty Position

The Department of Neurobiology and Physiology in the Weinberg College of Arts and Sciences seeks to recruit a new faculty member at the **Assistant Professor** level. Applicants holding a Ph.D or M.D. degree, and demonstrating an outstanding record of scientific achievement will be considered. We are interested in individuals whose research addresses fundamental issues in neuroscience and who show significant potential for innovation, scholarship, and commitment to excellence in research and teaching. Successful candidates will be expected to establish and maintain a high-profile research program attracting substantial extramural funding. The appointee will have access to state-of-the-art life science research support facilities and opportunities to interact with colleagues in the Institute for Complex Systems, Cognitive Neurology and Alzheimer's Disease Center, Center for Reproductive Science, Center for Sleep and Circadian Biology, Robert H. Lurie Comprehensive Cancer Center, and an interdepartmental neuroscience graduate program with over 150 faculty.

Applicants should submit a curriculum vitae and description of research plans to: **Search Committee Chair, Department of Neurobiology and Physiology, Northwestern University, 2205 Tech. Dr., Evanston, IL 60208 (www.northwestern.edu/neurobiology/)**. Three letters of recommendation should be sent to the same address. Applications received by **December 15, 2006** will be ensured full consideration.

Northwestern University is an Affirmative Action/Equal Opportunity Employer. Women and minority candidates are encouraged to apply.

CELL AND MOLECULAR BIOLOGIST
Southern Illinois University Edwardsville

CELL AND MOLECULAR BIOLOGIST: The Department of Biological Sciences, Southern Illinois University Edwardsville invites applications for a tenure-track position at the Assistant Professor level. We seek applicants with broad training in biological sciences and experience teaching cellular or molecular biology. The successful candidate will share responsibility for teaching a Cell and Molecular course for biology majors, offer upper division courses in his/her area of expertise, and may also participate in non-majors courses in biology. Candidates must also be able to contribute to the Department's Genetic Engineering program, and to the Biotechnology Management Master's program. Candidates should exhibit potential for independent and innovative research involving Master's and undergraduate students.

QUALIFICATIONS: A Ph.D. in Cell or Molecular Biology or in a related field with specialization in cell or molecular biology required at the time of hire. Relevant post-doctoral teaching and/or research experience preferred. Review of complete applications will begin on Jan. 8, 2007 and continue until the position is filled. To apply, send a letter of application with a statement of teaching philosophy, statement of research interests, *curriculum vitae*, copies of official transcripts, three letters of reference, and no more than three reprints to:

Chair, Cell and Molecular Search Committee
Southern Illinois University Edwardsville
Department of Biological Sciences
Box 1651S
Edwardsville, IL 62026-1651

SIUE is a comprehensive regional university located on a 2,660 acre campus in a semi-rural setting 25 minutes from downtown St. Louis, Missouri. SIUE is dedicated to excellence in undergraduate education.

SIUE is an Affirmative Action/Equal Opportunity Employer. SIUE is a state university - benefits under state sponsored plans may not be available to holders of F1 or J1 Visas.

Tenure-track Faculty Positions
Institute of Physics, Academia Sinica, Taipei

The Institute of Physics (**http://www.phys.sinica.edu.tw/**), Academia Sinica (**http://www.sinica.edu.tw/**) invites applications for several tenure-track faculty positions in all ranks. The Institute of Physics, currently consisting of forty-two faculty members, conducts research in (1) Basic and applied research in nano-sciences, (2) Non-linear and complex systems, statistical, computational and bio- physics, and (3) Intermediate and high energy physics. The position offers a free and superior research environment, an adequate startup research grant and good opportunities for interdisciplinary collaborations. Applicants should have an outstanding record of research achievements and will be expected to propose and pursue an independent research program.

Interested applicants should send a Curriculum Vitae and a list of publications, copies of five major publications, a summary of research achievements, a plan for future research, and three letters of recommendation to **Miss Ophelia Huang, Institute of Physics, Academia Sinica, Nankang, Taipei 11529, Taiwan; e-mail: ithuang@phys.sinica.edu.tw; phone: 886-2-27896718**. Review of applications will begin as soon as they are received and will continue until the positions are filled.

Academia Sinica in Taipei is the most prominent academic institution in Taiwan. While affiliated directly to the Presidential Office, Academia Sinica enjoys independence and autonomy in formulating its own research objectives. Its major tasks are to undertake in-depth academic research on various subjects in sciences and humanities. In recent years, under the leadership of the President of the institution, Dr. Yuan T. Lee (Nobel Prize winner in chemistry in 1986), Academia Sinica has transformed into a modern research institution. The Institute of Physics, being one of the institutes in the Academia Sinica, vows to conduct leading-edge research projects and to pursue excellence in its research programs.

Brown BioMed
DIVISION OF BIOLOGY AND MEDICINE

Faculty Position in Cardiovascular or Pulmonary Physiology
Assistant Professor

The Department of Molecular Pharmacology, Physiology and Biotechnology at Brown University invites applications for a tenure-track position in cardiovascular or pulmonary physiology. The anticipated start date is as early as July 1, 2007. Research space will be provided in a newly renovated laboratory with access to modern core facilities.

Applicants will be expected to develop an independent, externally funded research program in cellular and molecular physiology with translational applications to systems physiology; preference will be given to candidates with experience in cardiovascular or pulmonary physiology. Potential research programs of interest include cell growth and differentiation, gene expression, physiological genomics and proteomics, inflammation, or signal transduction. Collaborations with Brown Medical School affiliated hospitals are encouraged. Candidates should have a PhD and/or MD degree and relevant postdoctoral research training. Successful candidates must be committed to excellence in medical school, undergraduate, and graduate teaching in physiology.

Review of applications will commence on **December 1, 2006**, and will continue until the position is filled. Candidates should submit a curriculum vitae, recent representative publications, a description of career objectives, future research plans, a teaching statement, and three letters of recommendation either electronically to: **MPPB@brown.edu**, or by mail to: **Physiology Search Committee, Department of Molecular Pharmacology, Physiology and Biotechnology, Brown University, Box G-B3, Providence, RI 02912**. Electronic submission in pdf format is encouraged.

Brown University is an Equal Opportunity/Affirmative Action Employer and welcomes applications from women and minorities.

COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK

Tenure-Track Faculty in Developmental Neuroscience

The Columbia University Center for Neuroscience Initiatives, in conjunction with the Department of Psychiatry at Columbia and the Department of Developmental Psychobiology at the New York State Psychiatric Institute, is seeking applications for a new tenure-track faculty position in the area of Developmental Neuroscience. Candidates must have an M.D., Ph.D., or equivalent degree. The appointment is open to individuals at the level of Assistant or Associate Professor.

Applicants should have a demonstrated ability to conduct innovative, basic research that has the potential to contribute to translational investigations. Expertise in a broad range of neuroscience methodologies is highly desirable. These can include, but are not limited to, molecular neurobiology, neurogenetics, neuroanatomy, neuropharmacology, and electrophysiology. Areas of particular interest include developmental studies of neural circuits that underlie higher-level brain functions, and the regulation of emotional and/or cognitive states. Interest in genetic and environmental determinants of plasticity in neural systems will also be a useful area of emphasis.

Applicants should send their CV, a statement of research interests, and names of three referees to:

Bradley S. Peterson, M.D.
Columbia University Department of Psychiatry
1051 Riverside Drive, Unit 74, Room 2301
New York, NY 10032

E-mail: PetersoB@childpsych.columbia.edu

Columbia University takes affirmative action to ensure equal employment opportunity.

PHYSIOLOGY UCLA
Assistant or Associate Professor

The **Department of Physiology** at the **David Geffen School of Medicine at UCLA** invites applications for a tenure track faculty position, preferably at the level of Assistant or Associate Professor.

We are especially interested in candidates using molecular physiological approaches such as functional genomics, proteomics, molecular imaging, or systems biology. Areas of departmental strength include **molecular biophysics** and **cardiovascular research**, and candidates in these disciplines are encouraged to apply. However, we will consider applicants in all areas of modern physiology. Areas in which we might hope to expand include renal and respiratory physiology. Candidates are expected to have a strong background in cellular and molecular biology and a demonstrated interest in addressing fundamental physiological problems.

The successful candidate will be expected to develop an independent research program and participate in the teaching mission of the Department.

Interested applicants should email their curriculum vitae, a letter with a statement of research interests and career goals, and the names of three references to **Dr. Ernest Wright** at **PhysiologySearch@mednet.ucla.edu**. Applicants should also arrange for three letters of reference to be sent to Dr. Wright at the same email address.

UCLA is an Affirmative Action/Equal Opportunity Employer.
Women and minorities are encouraged to apply.

UCLA's Jonsson Comprehensive Cancer Center
David Geffen School of Medicine at UCLA
Established investigator in Basic and Translational Cancer Research

The UCLA Jonsson Comprehensive Cancer Center invites applications for a tenured/tenure-track faculty position. Investigators with basic research interests in areas such as cell cycle regulation, signal transduction, cancer biomarkers, metastasis, etc. – with a translational focus for investigator-initiated clinical trials – are encouraged to apply.

The position is a tenure-track professorship with a guaranteed salary base, outstanding fringe benefits, and substantial start-up funds. Applicants should have a research focus in a major epithelial cancer; i.e. lung, breast, prostate, colon.

Candidates for tenured Associate/Full Professor positions must have well established and funded research programs demonstrating translational potential. Assistant Professor applicants should have demonstrated their potential for research leadership. In all cases, emphasis will be placed on the applicant's record of research accomplishment, creativity, and promise of continuing success. Academic appointment(s) will be made in an appropriate department.

UCLA offers a highly collaborative research environment that promotes interactions between faculty in the School of Medicine, College of Letters and Sciences, School of Public Health, and School of Engineering. Research shared resources for flow cytometry, human and small animal imaging, high throughput molecular screening, DNA microarrays, cellular imaging and tissue processing, and human tissue banking are already established. In addition, a Clinical Research Support Unit provides a well-trained staff of clinical research nurses and data managers to facilitate clinical trials.

Candidates should forward 2 copies of (1) a description of their research background; (2) full curriculum vitae; and (3) a list of 3-5 references. Do not submit reprints at this time. Electronic submissions will not be considered. Materials should be sent to: **JCCC Search Committee, UCLA JCCC, 650 Charles E. Young Drive South, Box 951781, Los Angeles, CA 90095-1781**.

UC is an Affirmative Action/Equal Opportunity Employer.
All qualified candidates are encouraged to apply.

www.cancer.mednet.ucla.edu

ILLINOIS INSTITUTE OF TECHNOLOGY
Chair, Department of Biomedical Engineering

Illinois Institute of Technology (IIT) invites applications and nominations for the position of Chair of the Department of Biomedical Engineering. The university seeks a dynamic and vision-directed individual with proven leadership skills and an established history of excellence in both research and education pertinent to the field of biomedical engineering. Candidate must have an earned Ph.D. in biomedical engineering or related discipline. The new Chair will be expected to build on the successful educational programs within the department and work closely with the Pritzker Institute of Biomedical Science and Engineering at IIT to continue to grow research efforts.

The Department of Biomedical Engineering has grown rapidly in the five years since its inception to its current size of 10 full-time faculty members and approximately 160 undergraduate and 35 graduate students. The Institution is committed to significant growth of the department. The department occupies new teaching and research labs and will move into new office space in the Fall 2006. The Biomedical Engineering Department offers B.S. and Ph.D. degrees with educational and research efforts specializing in three tracks: Cell and Tissue Engineering, Medical Imaging, and Neural Engineering. These tracks are enhanced through close research and educational linkages with the University of Chicago, Argonne National Laboratories, and the Rehabilitation Institute of Chicago. Further information on the department can be found at **http://www.iit.edu/~biomed/index.html**.

IIT, founded in 1890, is a private Ph.D. granting, highly selective University with approximately 6,400 students enrolled in undergraduate and graduate programs including engineering, science, architecture, design, law, business, and psychology. The Main Campus is located on 120 acres, within minutes of downtown Chicago.

Applicants should electronically submit a letter of application, detailed CV and complete contact information for five professional references. Applications will be reviewed beginning **November 1, 2006** and will continue to be accepted until the position is filled. Submit applications, nominations, or general inquiries to: **Jamal S. Yagoobi, Chair, Mechanical, Materials and Aerospace Engineering, Illinois Institute of Technology, yagoobi@iit.edu.**

IIT is an Equal Opportunity and Affirmative Action Employer.

Assistant, Associate, and Full Professor Positions in the Department of Molecular, Cellular, and Developmental Biology and Graduate Program in Biomolecular Science and Engineering
University of California, Santa Barbara

The Department of Molecular, Cellular and Developmental Biology and the Interdisciplinary Graduate Program in Biomolecular Science and Engineering at the University of California, Santa Barbara invite applications for two open faculty positions.

- ***An Endowed Chair*** is to be filled at the advanced Assistant, Associate, or Full Professor rank. We seek an outstanding established scholar with an internationally recognized research program in any area of molecular, cellular, and developmental biology and/or biochemistry.
- ***Assistant Professor: Molecular Genetics/Developmental Biology.*** We seek outstanding candidates who are applying interdisciplinary approaches to fundamental biological problems. Applicants with an emphasis on developmental mechanisms, including stem cell biology, are especially urged to apply. This is a tenure-track position to be filled at the Assistant Professor rank.

Applicants for either position should submit curriculum vitae, selected reprints, a brief research plan, and, in the case of the Assistant Professor position, arrange for three letters of reference to be sent to: **Faculty Search Committee, Department of Molecular, Cellular and Developmental Biology, University of California, Santa Barbara, Santa Barbara, CA 93106-9610.** Review of applications will begin on **November 15, 2006**, and will continue until the positions are filled.

http://www.lifesci.ucsb.edu/mcdb/department/employment/employment.php

The department is especially interested in candidates who can contribute to the diversity and excellence of the academic community through research, teaching and service. UCSB is an Equal Opportunity Affirmative Action Employer.

OTOLARYNGOLOGIST

The Section of Otolaryngology - Head and Neck Surgery at Dartmouth-Hitchcock Medical Center seeks a board certified or board eligible Otolaryngologist for a full-time faculty position.The candidate should possess an interest in an academic career and in the education of medical students and residents.This position will combine a general otolaryngology with a subspecialty practice in otology or pediatric otolaryngology. Fellowship training in otology/ neurotology or pediatric otolaryngology is desirable. Research interests will be encouraged. Academic rank will be commensurate with qualifications and experience.

Interested applicants are encourage to send letters of inquiry and CV to:

Daniel Morrison, MD, Chairman
Section of Otolaryngology - Head & Neck Surgery
Dartmouth-Hitchcock Medical Center
One Medical Center Drive
Lebanon, NH 03756
Telephone: 603-650-8123

DARTMOUTH–HITCHCOCK
MEDICAL CENTER

Dartmouth-Hitchcock Medical Center is an affirmative action/equal opportunity employer and is especially interested in identifying female and minority candidates.

www.DHMC.org

McArdle Laboratory for Cancer Research
University of Wisconsin
School of Medicine and Public Health

Faculty Positions in Cancer Research

We are looking for two colleagues to join us in tenure-track faculty positions as Assistant Professor in the McArdle Laboratory for Cancer Research (http://www.mcardle.wisc.edu) at the University of Wisconsin School of Medicine and Public Health. The seventeen faculty at the McArdle Laboratory are committed to understanding the origins, prevention, and therapy of cancer through basic and translational research. Research areas of particular interest for this search include cancer genetics, cancer cell biology, tumor immunology, and the development of targeted therapies for the prevention or treatment of cancer, but candidates in all areas of basic cancer research will be considered. Members of the department participate in the University of Wisconsin Paul P. Carbone Comprehensive Cancer Center and in excellent, well-funded graduate and postdoctoral training programs. Faculty in the department have access to superb animal facilities, a genomics facility, a high-throughput small molecule screening facility, flow cytometry, experimental pathology, informatics, and biostatistics. Applicants are expected to have a Ph.D., M.D., or equivalent degree and significant research accomplishments. To be considered, please submit a curriculum vitae, publication list, a 2-3 page statement of research accomplishments and future objectives, and have 3 qualified individuals send letters of recommendation. Applications should be received by December 15, 2006 to ensure consideration.

Applications and letters of recommendation should be sent to: **Faculty Search Committee, McArdle Laboratory for Cancer Research, University of Wisconsin, 1400 University Avenue, Madison, WI 53706-1599.**

The University of Wisconsin is an equal opportunity/affirmative action employer. Minority and women candidates and all other qualified persons are encouraged to apply. Under Wisconsin statutes, names, positions and addresses of applicants and nominees may be subject to release upon request.

VirginiaTech
Invent the Future

Molecular Microbiologist

Department of Biological Sciences

The Department of Biological Sciences (**www.biol.vt.edu**) is recruiting a Molecular Microbiologist for a tenure track assistant professor faculty position. Competitive salary and start-up package will be provided. The department is interested in hiring an individual from one of several research areas, including but not limited to: (1) Infectious disease; (2) Microbial interactions with the environment; (3) Signal transduction; and (4) Prokaryotic development. The hire may become affiliated with the Institute for Biomedical and Public Health Sciences or the Institute for Critical Technology and Applied Science, which were created to increase research training and research funding through interdisciplinary initiatives. Core laboratory facilities are available for DNA sequencing, microarrays, proteomics, protein structure analysis and high speed computation.

Applicants should submit a cover letter, curriculum vitae, and a statement of research and teaching interests emphasizing career goals using our on-line system (**https://jobs.vt.edu**, search posting **061107**). Three reference letters should be sent to the chair of the search committee, **Dr. Ann Stevens; Department of Biological Sciences; 2119 Derring Hall MC0406; Virginia Tech; Blacksburg, VA 24061**. Inquiries concerning the position or application process should be directed to the chair of the search committee (**ams@vt.edu**; **540-231-9378**). Review of applications will begin **December 1, 2006** and continue until position is filled.

Virginia Tech is an NSF Advance Institution and has a strong commitment to the principle of diversity and, in that spirit, seeks a broad spectrum of candidates, including women, minorities, and people with disabilities.

Washington University in St. Louis

ASSISTANT PROFESSOR IN PLANT BIOLOGY

Faculty Position in Plant Biology
Department of Biology

The Department of Biology at Washington University is seeking a colleague working in the area of Plant Biology for a newly created and approved search at the rank of tenure-track Assistant Professor. Under exceptional circumstances, tenured appointments may be considered at the rank of associate or full professor. Candidates should have a Ph.D., significant research accomplishments and a commitment to pursue innovative approaches to study plants, as well as a dedication to excellence in both graduate and undergraduate education. Areas of interest include cell biology, development and biochemistry, especially programs that take advantage of systems and imaging approaches. Participation will be encouraged in interdisciplinary research within the plant biology community (**http://www.biology.wustl.edu/plant/plantbiology.php**), which includes the Donald Danforth Plant Science Center (**http://www.ddpsc.org/**), and within the broader life science community at Washington University (**http://dbbs.wustl.edu/**).

Review of applications will begin **November 13, 2006**. Applications will be accepted until the position is filled. Please submit a cover letter, curriculum vitae, brief statements of research and teaching interests, reprints of up to three papers, and the names and affiliations of three persons who have been asked to send letters of recommendation. We prefer electronic submissions, which can be submitted to the following e-mail address: **plantsearch2006@biology.wustl.edu**. If preferred, hard copy application can be mailed to the following address: **Plant Science Search Committee, Department of Biology, Washington University, Campus Box 1137, One Brookings Drive, St. Louis, MO 63130-4899.**

Washington University is committed to excellence through diversity, and we particularly encourage applications from persons from underrepresented groups. Washington University is an Affirmative Action Employer.

FACULTY POSITIONS IN NEUROSCIENCE AND DEVELOPMENTAL BIOLOGY

The Department of Cell and Molecular Biology at Tulane University (**http://cell.tulane.edu/**) anticipates filling two tenure-track positions beginning July 1, 2007, at the level of Assistant Professor. These positions are subject to a final university determination on funding. Targeted are individuals with research interests focused in either Cellular/Molecular Neuroscience or Developmental Biology. The Department is undergoing a rebuilding process and has targeted these areas for rapid growth. Applicants must have a Ph.D., at least 2 years of postdoctoral experience, a strong publication record, and show strong potential for obtaining external funding. The successful applicant will be expected to establish a vigorous, independent research program and to participate in graduate and undergraduate teaching. Opportunities exist for research collaborations and participation in the Tulane Cancer Center, the Tulane Primate Center, the Center for Bioenvironmental Research, and the Tulane Neuroscience Program.

Applicants should send curriculum vitae, a brief statement of research interests and three letters of recommendation by **December 1, 2006** to: **Dr. David Mullin, Chair, Department of Cell and Molecular Biology, Tulane University, 2000 Percival Stern Hall, New Orleans, LA 70118.**

Tulane University is an Equal Opportunity/ Affirmative Action Employer and encourages minority and female applicants to apply.

Tenure Track Research Positions in Prokaryotic Biology

The Wadsworth Center is seeking outstanding scientists at all levels to establish competitive research programs in all areas of prokaryotic biology, including, but not limited to:

- **Cell Biology**
- **Gene Regulation and Signaling**
- **Host-Pathogen Interactions**
- **Molecular Genetics**
- **Biology of Bacteriophages**
- **Pathogenesis**

The Wadsworth Center enjoys a century of excellence as a research-intensive institution and is the country's most comprehensive state public health laboratory. The Center has a staff of 1,100, including 175 doctoral-level scientists, and for several years has been nationally recognized as a "Best Place to Work" for both faculty and postdoctoral fellows. The Center provides a dynamic research environment focused on infectious, genetic and environmental diseases and their impact on human health.

Wadsworth scientists receive competitive start-up packages and access to outstanding core facilities. Wadsworth Center also is the home of the Department of Biomedical Sciences, a vibrant graduate program affiliated with the University at Albany, SUNY (www.wadsworth.org/bms). Successful candidates are expected to join the faculty and mentor graduate students in the Department.

Applicants must possess a Ph.D., M.D. or equivalent. Review of applicants will begin November 1, 2006. Applicants should submit a curriculum vitae and a summary of research interests and future plans, via email (Word or PDF file), and arrange to have three reference letters sent to: prokaryot@wadsworth.org or Dr. Keith Derbyshire, Wadsworth Center, New York State Department of Health, PO Box 22002, Albany, NY 12201-2002. AA/EOE

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New York State Department of Health
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Four Assistant Professor Positions in Biology San Francisco State University

The Department of Biology at San Francisco State University invites applications for four tenure-track positions at the rank of Assistant Professor.

Animal Ecology/Evolutionary Biology. We seek applications from outstanding researchers whose work emphasizes the study of ecology and evolution using animals, especially birds, mammals, and non-insect invertebrates. The candidate will teach upper-division and graduate courses in ecology or evolution.
Microbiology. We seek an individual with a strong record of research using contemporary molecular approaches to investigate microbial physiology, genetics, pathogenesis or social behaviors. Responsibilities include teaching undergraduate and graduate courses in microbiology.
Plant Physiological Ecology. We seek exceptional researchers in plant ecology/physiology, especially those who consider physiological questions in an ecological context, integrating experimental field and laboratory studies with theory. The candidate will teach upper-division and graduate courses in ecology or plant physiology.
Animal Physiology. We seek superior researchers in all areas of vertebrate or invertebrate physiology, especially those whose interests complement existing departmental strengths in endocrinology, neurobiology, and ecological physiology. Responsibilities include teaching in the undergraduate and graduate physiology programs.

Qualifications for all positions are a Ph.D. degree and postdoctoral training. Teaching experience is desirable. Candidates must be strongly committed to teaching, mentoring of undergraduate and graduate (MS) students, and developing a competitive, externally funded research program. Candidates may participate in team-teaching of introductory-level and lower-division courses. Send curriculum vitae, separate statements of research and teaching interests, copies of significant publications, and three reference letters to: **Chair, [Relevant Position] Search Committee, Dept. of Biology, San Francisco State University, 1600 Holloway Ave., San Francisco, CA 94132**. Review of applications begins **15 November 2006** and continues until suitable candidates are chosen. For additional information about the Department of Biology, please visit our web site at **http://www.sfsu.edu/~biology**.

SFSU and the Department of Biology are strongly committed to a diverse professoriate that includes women and individuals from underrepresented minority groups. SFSU is an EEO/AA Employer.

University of Minnesota-Twin Cities Department of Biochemistry, Molecular Biology and Biophysics Macromolecular Crystallography

The University of Minnesota is seeking outstanding candidates for a full-time, tenure-track position to begin on or about July 1, 2007. The expected appointment is as a tenure-track assistant professor, but candidates at a higher level are encouraged to apply. The new appointment will enhance our strengths in biophysics and structural biology. Superb facilities for x-ray data collection (**http://www.mbc-als.org/**, **http://cbs.umn.edu/bmbb/structbio/facilities/crystallography.html**) and for computation (**http://www.msi.umn.edu/bscl/**) are available.

All applicants must have a Ph.D. and/or M.D. degree. Successful candidates must be a U.S. Citizen or be able to secure permanent resident status. The successful candidate will be expected to develop strong, externally funded research programs and contribute to the undergraduate, graduate and professional teaching programs of the department. Candidates who can interact collaboratively among a variety of disciplines are strongly desired.

The new position includes a substantial start-up package and a salary commensurate with education and experience. Review of applications will continue until the position is filled. To apply please send curriculum vitae, a brief statement of current and future research, and three letters of recommendation that consider both research and teaching potential. Please send these items as email attachments to **swans143@umn.edu** or address these materials to **Professor Douglas H. Ohlendorf, Head of Search Committee, c/o Ms. Ann Johnson, University of Minnesota, Department of Biochemistry, Molecular Biology and Biophysics, 6-155 Jackson Hall, 321 Church St. SE, Minneapolis MN 55455**.

At the University of Minnesota, molecular and cellular biology is a research focus of the institution. This has resulted in a rapid expansion within the biological sciences, and a number of new dedicated research buildings have been constructed. In addition, the Twin Cities are a focus for the performing arts and Minnesota offers a broad spectrum of outdoor activities during all seasons.

The University of Minnesota is an Equal Opportunity Educator and Employer.

Faculty Positions
Division of Cell Biology, Microbiology and Molecular Biology
University of South Florida

The Division of Cell Biology, Microbiology, and Molecular Biology (CMM) of the Department of Biology at the University of South Florida (USF) is hiring four tenure-track faculty as part of a major expansion. At least two of the positions will be at the Assistant Professor level; however outstanding candidates at the Associate or Full Professor level are encouraged to apply. Teams of multiple candidates with related research will also be considered. Three positions are in the general area of **Proteomics/Genomics**. Successful candidates for these positions will use proteomics and/or genomics to study some aspect of cellular function and to complement current faculty research in the areas of genome instability, evolution, development, signal transduction and transcriptional regulation. These positions are contingent on available funding. One position is in the area of **Molecular Microbiology**. The successful candidate for this position will bring expertise and research interests in microbial genetics, molecular virology, molecular pathogenesis, or similar areas of microbiology. Successful candidates for this position will complement current faculty and University strengths in biosensor and molecular detection technologies and biodefense. Faculty hired for these positions will be expected to develop and maintain strong, externally-funded research programs, teach at the graduate and undergraduate levels and direct Ph.D. and M.S. graduate students. USF is designated by the Carnegie Foundation as a Research University/Very High Research Activity and has a rapidly increasing research base in the biomedical sciences. Opportunities for collaboration exist with the Departments of Chemistry and Physics in the College of Arts and Sciences, with the USF Colleges of Medicine, Public Health, and Engineering and with the H. Lee Moffitt Cancer Center and Research Institute.

Applicants should submit a letter of application, curriculum vitae, research plan, and statement of teaching interests and arrange for three letters of recommendation to be sent to: **Proteomics/Genomics Search Committee or Molecular Microbiology Search Committee, CMM Division, Department of Biology, University of South Florida, 4202 E. Fowler Avenue, SCA110, Tampa, FL 33620-5200**. Review of applications will begin on **December 8, 2006**, and will continue until the positions are filled.

The University of South Florida is an Equal Opportunity/Affirmative Action/ Equal Access Institution. For disability accommodations, contact Dawn McGowan at (813)974-8088 to make appropriate arrangements.

UNIVERSITY of ARKANSAS
1871

ENDOWED CHAIR, GLOBAL CHANGE BIOLOGY

The Department of Biological Sciences seeks applicants for an Endowed Chair (rank open) in Global Change Biology, working on the biotic consequences of environmental change. Candidates must have a Ph.D. and an established record of research productivity in a field relevant to Global Change Biology. The candidate will be expected to continue a well funded research program, supervise graduate students, teach at the graduate and undergraduate levels, and provide leadership at the department and university levels in developing research emphases in Global Change Biology.

ECOLOGIST

The Department of Biological Sciences seeks applicants for a tenure-track Assistant Professor in Ecology. Particular preference will be paid to those working in problems that emphasize community, ecosystem, or landscape ecology. The candidate must have a Ph.D., postdoctoral experience and an established record of research productivity and will be expected to develop an active research program, supervise graduate and undergraduate research, and teach at the graduate and undergraduate levels.

The University of Arkansas is a land grant institution with facilities for stable isotope analysis, molecular biology, GIS, tree-ring analysis, water and soil analyses, and the USGS Cooperative Fish and Wildlife Research Unit.

Application review will begin **November 15, 2006**, and will continue until the positions are filled. Send a curriculum vitae, statements of research and teaching interests, and at least three letters of recommendation to: **Dr. Steven J. Beaupre, GCB Search Committee Chair, Department of Biological Sciences, or Dr. Gary R Huxel, Ecology Search Committee Chair, SCEN 632, University of Arkansas, Fayetteville, AR 72701**. Please visit **http://biology.uark.edu/**.

The University of Arkansas is an Equal Opportunity/Affirmative Action Employer. Applicants must have proof of legal authority to work in the United States at the time of hire.

Dream. Challenge. Succeed.

NEUROSCIENCE ASSISTANT/ASSOCIATE/ PROFESSOR POSITIONS

The Department of Anatomy & Neurobiology announces the availability of TWO tenure track positions at the ASSISTANT, ASSOCIATE or FULL PROFESSOR levels. The positions are for individuals with outstanding research programs in translational neuroscience, with emphasis on CNS degenerative and regenerative processes. Applications are invited from creative, successful individuals who want to contribute to dynamic, growing research and academic programs within a comprehensive Medical Center. Successful candidates are expected to develop and maintain innovative, nationally recognized research programs and/or academic programs. Competitive start-up funds, salaries and state-of-the-art facilities are available. Special consideration will be given to applicants who complement existing departmental strengths and who will significantly contribute to the department's teaching mission. Applicants must have a PhD or MD or equivalent degree and should have two years of postdoctoral or other relevant experience. Interested individuals should send curriculum vitae, a summary of past experience and future research plans. The Search Committee is currently reviewing applications and will continue until the positions are filled. Applications and nominations should be forwarded to:

Don M. Gash, Professor and Chair
Department of Anatomy & Neurobiology
317 Whitney Hendrickson Bldg. (MRISC)
University of Kentucky
Lexington, KY 40536-0098
Email: dongash@email.uky.edu
http://www.mc.uky.edu/neurobiology/

UK
UNIVERSITY OF KENTUCKY
College of Medicine
Department of Anatomy and Neurobiology

The University of Kentucky is an equal opportunity employer and encourages applications from minorities and women.

COMMUNITY ECOLOGY
LOYOLA MARYMOUNT UNIVERSITY

The Department of Biology seeks a broadly trained community ecologist for a tenure-track position at the rank of Assistant Professor. The successful candidate will possess a Ph.D. in Biology, Botany, Zoology or equivalent, plus strong interest and capability in field-oriented research and teaching. Teaching responsibilities include lower division courses, upper division courses in field ecology and in the candidate's area of specialization, and a senior-level seminar. The successful candidate must develop an active research program which involves undergraduates. University and department service and scholarly publication are required.

Loyola Marymount University, established in 1911, is the only Jesuit University in southern California. Over 6,000 students are enrolled in the Colleges of Liberal Arts, Business Administration, Science and Engineering, Communication and Fine Arts, the Schools of Education and Film and Television, and the Law School. The campus is situated on a bluff overlooking the Pacific Ocean and LA's west side and is from minutes to half a day's travel to beach, dune, mountain, chaparral, desert, wetlands, marine and California Channel Islands communities. The department also maintains a biological station in Baja California, Mexico. The Biology Department has 12 faculty dedicated to undergraduate teaching and research and welcomes candidates who desire to work in such an environment. Faculty are also engaged in an interdisciplinary effort in biomathematics; the community ecologist's participation would be welcomed. The department is housed in a renovated science building which includes facilities equipped for supporting field and laboratory research.

The University particularly invites applicants who desire to participate in a mission based on the Jesuit and Marymount traditions of higher education. Send letter of application, curriculum vitae, graduate transcripts, selected publications, and three letters of reference by **November 1, 2006**, to: **Ecology Search Committee, Department of Biology, Loyola Marymount University, 1 LMU Drive, MS 8220, Los Angeles, CA 90045-2659**. For additional information, contact **Dr. Martin G. Ramirez**, **(310) 338-5120**. Salaries are competitive and commensurate with background and experience.

LMU is an Equal Opportunity Employer.
Women and Minorities are strongly encouraged to apply.

UNIVERSITY MEDICAL CENTER
THE UNIVERSITY OF TOLEDO

Faculty Position, Cancer Biology

Applications are invited for a tenure-track position at the Assistant or Associate Professor level. Applicants working at the cellular, molecular or genetic levels on projects related to the causes, progression, diagnosis or treatment of cancer are encouraged to apply. Appointment will be in the Dept. of Biochemistry and Cancer Biology in the University of Toledo College of Medicine. Cancer research has been targeted for strategic emphasis, and excellent facilities, start-up packages, and collaborative opportunities are available. Research areas currently represented in the department include signal transduction, protein trafficking, DNA damage/repair, development of gene therapy vectors, and regulation of genes involved in cell growth, cell differentiation, and programmed cell death. Applicants should have a Ph.D. or M.D. degree with postdoctoral research accomplishments. Successful candidates will be expected to maintain a vigorous externally funded research program and participate in the educational missions of the medical and graduate colleges. Applications should include: a CV, description of research plans, copies of selected publications, and contact information for three references. Materials may be sent via regular mail or e-mail (PDF format) to: **Biochemistry and Cancer Biology Search Committee, c/o Jenifer Zak, Department of Biochemistry and Cancer Biology, Mail Stop #1010, Health Science Campus, 3000 Arlington Ave., Toledo, OH 43614-2598; jenifer.zak @utoledo.edu.** *University of Toledo is committed to diversity and equal opportunity. Applications from women and minority candidates are strongly encouraged.*

ILLINOIS
1867
UNIVERSITY OF ILLINOIS AT URBANA-CHAMPAIGN

FACULTY POSITIONS IN BIOENGINEERING
Department of Bioengineering

The Department of Bioengineering at the University of Illinois at Urbana-Champaign (UIUC) seeks full-time Bioengineering faculty for tenured or tenure-track positions. Relevant areas of expertise include Cell and Molecular Engineering, Micro/Nano/Molecular Technologies in Bioengineering, and Molecular probes for Bioimaging and Pharmaceutics, especially with applications to Cancer, Neuroscience, and Animal Models of Disease. Successful candidates will be expected to carry out independent research and to perform academic duties associated with our B.S., M.S., and Ph.D. programs.

The University of Illinois at Urbana-Champaign (UIUC) offers exceptional opportunities for innovative individuals to conduct collaborative research at the forefront of bioengineering including possible affiliations with the Beckman Institute for Advanced Science and Technology, the Biotechnology Center, the Institute for Genomic Biology, the Seitz Materials Research Laboratory, the Micro and Nanotechnology Laboratory, and the National Center for Supercomputing Applications (NCSA).

Minimum qualifications include an earned doctorate in Bioengineering or related fields, outstanding academic credentials, and the ability to teach effectively at both the graduate and undergraduate levels. Searches are open to all levels. Senior faculty applicants are particularly encouraged to apply. Rank and salary will be commensurate with qualifications. Starting dates for these positions are negotiable.

For further information call **217-333-1867**, email **bioen@uiuc.edu**. To apply, please visit the website **http://my.bioen.uiuc.edu/join**. To ensure full consideration, applications should be received by **December 1, 2006**.

The University of Illinois is an Affirmative Action/Equal Opportunity Employer.

New York University

FACULTY POSITIONS
Department of Biology

Center For Comparative Functional Genomics

NEW YORK UNIVERSITY
CENTER FOR COMPARATIVE
FUNCTIONAL GENOMICS

As part of a multi-year hiring plan, New York University's Center for Comparative Functional Genomics in the Department of Biology invites applications for multiple faculty positions (rank open) to begin September 1, 2007, or as negotiated, pending budgetary and administrative approval. Candidates using high throughput approaches and computational methods to investigate biological regulatory mechanisms and their evolution at the level of systems and networks are especially encouraged to apply. Candidates will be expected to have or develop active, externally funded research programs and to participate in the department's teaching activities at both the undergraduate and graduate levels. The Center and the Department (http://www.nyu.edu/fas/dept/biology) offer an outstanding and collegial research environment and opportunities for active collaborations with other related divisions within the university including the NYU Courant Institute's Departments of Mathematical and Computer Science and with genomic consortia formed with other New York institutions.

Applications should include cover letter, research statement, curriculum vitae, and three letters of reference. Electronic applications as PDF files should be sent to **biology.recruitment@nyu.edu**. or **Chair of the Search Committee, New York University, Center for Comparative Functional Genomics, Department of Biology, New York University, 1009 Silver Center, 100 Washington Square East, New York, N.Y. 10003**. *Deadline will be* ***November 30, 2006***.

NYU is an Equal Opportunity/Affirmative Action Employer.

Assistant/Associate Professor in
SYSTEMS BIOLOGY

The Department of Systems Biology at Harvard Medical School invites applications for the position of Assistant or Associate Professor. Areas of particular interest to the Department include spatial organization and homeostasis in tissues and embryos, and the effects of drugs on biological networks. Technology research areas of special interest include methods for tracking the state or abundance of specific molecules in single cells or in living tissues, or for integrating high-dimensional data sets with mechanistic models.

The Department is a supportive and congenial environment for researchers originally trained in quantitative or theoretical disciplines who are now interested in important biological or medical problems, as well as for biologists with strong interests in modeling approaches or quantitative measurement. We place particular emphasis on mentoring young faculty, supporting risky or innovative research programs, and helping young faculty address the challenges of balancing family life with work.

Applications should include a CV and a research proposal and should be sent to: **Timothy J. Mitchison, PhD, Chair, Systems Biology Search Committee, Harvard Medical School, 200 Longwood Ave, WAB-536, Boston, MA 02115.**

Please arrange for three letters of reference to be sent to the same address. PDF submissions are also acceptable and should be e-mailed to: **SystemsBiology_Search@hms.harvard.edu**

Harvard University is an Affirmative Action/Equal Opportunity Employer. Women and minorities are particularly encouraged to apply.

The Life Sciences Institute and the University of Michigan Medical School invite applications for tenure track **ASSISTANT PROFESSOR** positions. We are seeking outstanding scholars, with Ph.D., M.D. or equivalent degrees and relevant postdoctoral experience, who show exceptional potential to develop an independent research program that will address fundamental issues in any aspect of stem cell biology. Applicants who have already established successful independent research programs will be considered for tenured **ASSOCIATE PROFESSOR** or **PROFESSOR** positions.

Applicants should send a curriculum vitae, copies of up to three reprints, a one- to two-page summary of research plans, and arrange to have three letters of reference sent directly by November 1, 2006 to: **Stem Cell Search Committee, c/o Rebecca Fritts, Life Sciences Institute, University of Michigan, 210 Washtenaw Avenue, Ann Arbor, Michigan, 48109-2216**.

The University of Michigan is an Affirmative Action/Equal Opportunity Employer.

ASSISTANT PROFESSOR POSITION
PANCREATIC ISLET DEVELOPMENTAL BIOLOGY/ STEM CELL BIOLOGY

The Barbara Davis Center for Childhood Diabetes is the largest diabetes and endocrine care program in the Colorado community. Its basic research program focuses on immunology and genetics of type I diabetes, developmental and cell biology of the pancreas and transplantation immunobiology. The BDC recently moved to a new 100,000ASF building on the UCDHSC Fitzsimons campus in Denver, Colorado and is seeking faculty recruits in developmental biology and stem cell biology as part of a campus-wide funded initiative in regenerative medicine

The successful applicant is expected to hold a PhD or equivalent degree, to have an outstanding record of accomplishments in biomedical research. The appointee will establish a vigorous and independent research program in the area of developmental biology of the pancreas or stem cell biology and to contribute to the educational mission of the university. The appointment is supported by generous startup funds and space and will initially be for 3 years then subject to review for tenure track development.

Applications should include a curriculum vitae and the names of three or more references, a summary of research experience and a statement of proposed research directions addressed to: **John C Hutton PhD, c/o Emily Warren, Barbara Davis Center for Childhood Diabetes, University of Colorado at Denver and Colorado Health Sciences Center, Mail Stop B140, P.O. Box 6511, Aurora, CO 80045**. Applications are acceptable as email attachments to **Emily.Warren@uchsc.edu**.

The University of Colorado is committed to diversity and equality in education and employment.

FACULTY POSITION IN DEVELOPMENTAL BIOLOGY

The University of Georgia invites applicants for a tenure track Assistant Professor position in developmental biology. Applicants from any area of developmental biology are welcome; those working in mouse and/or zebrafish are especially encouraged to apply. The successful candidate's laboratory will be housed in the new Coverdell Center in an interactive, interdisciplinary faculty group with diverse research interests that provide a supportive environment for developmental biology research. The Coverdell Center has state of the art animal facilities for mouse and zebrafish research. The position includes a competitive salary, excellent laboratory space, and a generous start-up package. The successful candidate will be expected to develop a strong extramurally funded research program, and contribute to teaching in the department of appointment. This position is part of a planned multi-position expansion of the Interdepartmental Developmental Biology Group at UGA, which currently includes faculty from seven departments. Departmental affiliation will depend on the candidate's research focus. For more on the Developmental Biology Group at UGA, see **http://devbio.uga.edu**.

Applications received by January 5, 2007 are assured of full consideration. Please email a CV, research and teaching statements, the names of three references, and up to three publications (all in PDF format please) to **pabond@uga.edu**. Emailed letters are acceptable if followed by an original. Letters of recommendation should be mailed to:

Dr. Nancy R. Manley
Associate Professor and Chair
Developmental Biology Group
S270A Coverdell Center for Biomedical and Health Sciences
University of Georgia, Athens, Georgia 30602

The Franklin College of Arts and Sciences is highly committed to increasing the diversity of its faculty and strongly encourages applications from members of under-represented groups. The University of Georgia is an Affirmative Action/Equal Opportunity Employer

CAL POLY

San Luis Obispo
CA 93407

ANIMAL PHYSIOLOGISTS

The Biological Sciences Department within the College of Science and Mathematics at Cal Poly, San Luis Obispo, California is seeking two full-time, academic year, tenure-track Animal Physiologists at the assistant professor rank beginning September 2007. Teaching responsibilities may include human anatomy and physiology, general physiology, introductory biology, histology, graduate level organismal biology, or other undergraduate and graduate courses as appropriate to background and training. The position is open to all specialties; desirable research areas include neurophysiology, endocrine physiology, comparative physiology, and integrative systems physiology. The successful candidate must have a strong commitment to undergraduate and graduate teaching, curriculum development, and implementation of a student-centered research program. Ph.D. in related field required at time of hiring. Salary is commensurate with qualifications and experience.

To apply, visit **WWW.CALPOLYJOBS.ORG**, complete a required online faculty application and submit to Requisition **#101098**; attach your curriculum vitae, statement of teaching philosophy, and statement of professional goals. Also mail a hard copy of the above noted documents and arrange to have official graduate transcripts, and three letters of recommendation sent to: **Dr. Michael Yoshimura, Chair, Biological Sciences Department, California Polytechnic State University, San Luis Obispo, CA 93407-0401**. Review of applications will begin **November 20, 2006**. Applicants are strongly encouraged to have all materials submitted by **November 20, 2006**; applications received after this date may be considered. For questions, contact the Biological Sciences Department at **(805) 756-5242**.

Cal Poly is strongly committed to achieving excellence through cultural diversity. The university actively encourages applications and nominations of all qualified individuals. EEO.

University of Nebraska Medical Center Department of Genetics, Cell Biology and Anatomy

ASSISTANT/ASSOCIATE/FULL PROFESSORS

Cancer Genetics/Genomics
Developmental Genetics/ Genomics
Regenerative Biology

Applications are invited from established investigators using genetics/genomics based approaches in the study of cancer, development or regenerative biology. Those recruited to these positions will be expected to maintain an independent research program and participate in the educational programs of the University. Outstanding start-up resources, laboratory facilities and shared laboratory resources are available. Individuals working in cancer related areas will have the opportunity to become a member of the UNMC Eppley Cancer Center, a National Cancer Institute-designated cancer center. Omaha offers an outstanding school system, moderate cost of living, and numerous cultural and recreational activities. Applicants with a Ph.D., M.D., or other doctoral degree are invited to submit their curriculum vitae, a concise summary of their ongoing/future research and the names of three or more references to: **Dr. James Shull, Department of Genetics, Cell Biology and Anatomy, University of Nebraska Medical Center, 985805 Nebraska Medical Center, Omaha, NE 68198-5805**. Review of applications will begin **November 1, 2006**. *The University of Nebraska is an Equal Opportunity/Affirmative Action Employer. Individuals of culturally diverse backgrounds and women are encouraged to apply.* **http://www.unmc.edu/genetics**.

Biomedical Engineering Faculty Positions in Computational BioNetworks and Systems Biology of Human Nutrition at the University of California, Davis

The College of Engineering at UC Davis invites applications from qualified candidates for two tenure-track faculty positions at the assistant professor level in the Department of Biomedical Engineering (BME). The first will focus on computational approaches to the elucidation and exploitation of biological networks at the cell and molecular level. This position is one of seven in the campus-wide Computational Characterization and Exploitation of Biological Networks Initiative (**www.cnb.ucdavis.edu**). The second will focus on the elucidation, characterization and quantitative systems integration of the underlying mechanisms by which diet may promote health or lead to disease. This position, which is joint between the Departments of BME (80%) and Nutrition (20%), is part of the campus-wide Foods for Health Initiative. In each case, the hire would be expected to work collaboratively with other faculty hires under the initiative. Candidates should have a Ph.D. degree in biomedical engineering or a related field, a commitment to excellence in teaching and a publication record that demonstrates excellence in research. The hires will be expected to develop an extramurally funded research program, to contribute to core undergraduate and graduate courses and to assist in establishing an innovative multidisciplinary curriculum in the field of quantitative systems biology.

UC Davis is 14th among US universities in research funding and is ranked among the top ten public engineering colleges in the nation. Davis is a pleasant, family-oriented community in a college-town setting with excellent public schools and a mild climate. Davis is ideally just 15 miles from California's capital city of Sacramento and is within easy driving distance of the Sierra Nevada Mountains, San Francisco, Berkeley, Silicon Valley, wine country and the Pacific Coastal areas.

Interested candidates should submit all materials via the web-based online submission system (**https://jobs.bme.ucdavis.edu**). Required materials include a statement of research and teaching interests (this should include information about mentoring women, minorities, students with disabilities, or other under-represented groups), a curriculum vitae, three to five representative publications and the names and contact information of at least five referees who have agreed to write letters of reference. Inquiries can be directed to the chair of the search committee at **biomedicalengineering@ucdavis.edu**. The review of applications will begin on **December 15, 2006**. However, the positions will remain open until filled. The UC Davis College of Engineering is committed to building a diverse faculty, staff and student body as it responds to the changing population and educational needs of California and the nation. **http://engineering.ucdavis.edu/**.

The University of California is an Affirmative Action/Equal Opportunity Employer.

COLUMBIA UNIVERSITY

Department of Biological Sciences

The Department of Biological Sciences of Columbia University invites applications for a tenure-track appointment at the Assistant Professor level in the areas of Developmental, Cell, and Molecular Biology. We are looking for an individual who has an outstanding and innovative research record and plan. Areas of particular interest include cancer and vertebrate development, but we also welcome applications from other areas that complement the diverse interests and approaches of current faculty. The successful candidate will possess a Ph.D. in a relevant discipline and have already demonstrated an outstanding record of research. We expect that the successful candidate will develop a vigorous research program and teach in undergraduate and graduate programs.

Send CV, statement of research goals, and three letters of reference by November 30, 2006, by e-mail (preferred) to:

biologysearch@biology.columbia.edu

or mail to:
Developmental, Cell, and Molecular Biology Search
Department of Biological Sciences
Columbia University
600 Fairchild, MC2402
1212 Amsterdam Avenue
New York, NY 10027

Columbia University is an equal opportunity/affirmative action employer.
Minorities and women are encouraged to apply.

RuG

MSC plus Materials Science Centre

Faculty of Mathematics and Natural Sciences

Professor of Polymer Science

The Faculty of Mathematics and Natural Sciences of the University of Groningen is seeking applications and nominations for the position of full or associate professor of polymer science. The Faculty offers Bachelor, Master and Ph.D. programmes over the entire range of natural sciences. The research in the Faculty is organized in research institutes. The vacancy exists within the research institute Materials Science Centre^{plus} (MSC^{plus}), which unites 21 research groups in physics, chemistry, and biology. The MSC^{plus} is one of six recognized National Centers of Excellence in The Netherlands. Its mission is design and functionality of novel materials, with a focus on understanding and control at the microscopic level. The Centre thrives on a strong interdisciplinary nature of its research programme and frequent collaborations between its various groups.

We are seeking candidates who are highly qualified in the field of polymer chemistry, preferably with a focus on the development of modern smart and functional polymer materials to arrive at a wide range of new applications. Research in this field requires a multidisciplinary approach and candidates will be polymer scientists with a broad experience in order to be able not only to survey the synthesis of polymer materials but also to connect the chemistry with the properties of the molecules and materials.

The complete text of the advertisement can be found on MSC^{plus} website at **www.rug.nl/msc/vacancies/atmsc/otherVacancies**

Review of application will begin November.24, 2006, and will continue until the position is filled. Application in hard copy should be addressed to: Prof. J. Knoester, MSC, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands; By E-mail (Word or PDF) to: m.h.derix@rug.nl

MOUNT SINAI SCHOOL OF MEDICINE

Assistant or Associate Professor Position Black Family Scholar

The newly established Black Family Stem Cell Institute at the Mount Sinai School of Medicine of New York University is recruiting faculty at the level of Assistant or Associate Professor. Areas of interest include, but are not limited to, embryonic stem cell biology, mouse development, and regenerative processes in adult tissues. Applicants should have outstanding ongoing federally funded research programs (Associate Professor level) or have demonstrated substantial scientific productivity during postdoctoral training (Assistant Professor level).

The Black Family Stem Cell Institute is an interdepartmental institute that provides an outstanding interactive environment for the development of highly competitive research programs in both embryonic and adult stem cell biology within the Mount Sinai School of Medicine (**www.blackfamilystemcell.org**). The School of Medicine has state-of-the-art core facilities, including microarray, mouse genetics, microscopy, microsurgery, flow cytometry and a newly established training facility for human embryonic stem cell research. The successful applicant will be appointed as Black Family Scholar in an appropriate department within the school.

Applications should include CV, a brief description of current research and future research plans, 3-5 key reprints and names and contact information for 3 referees. Please send applications to:

Dr. Margaret H. Baron or Dr. James J. Bieker
c/o Ms. Denise James
The Mount Sinai School of Medicine
Department of Molecular, Cell and Developmental Biology
One Gustave L. Levy Place
Box 1020
New York, NY 10029

Penn
University of Pennsylvania

Faculty Position in Neurobiology

The Biology Department of the University of Pennsylvania invites applicants for a tenure track position in the area of Neurobiology, with a focus on individuals whose research spans from genes to brain to behavior. We anticipate that this appointment will be made at the Assistant Professor level, but outstanding senior candidates will be given serious consideration. We are particularly interested in individuals carrying out mechanistic studies aimed at defining the role of specific genetic networks or neural circuits in behavior. Suitable experimental approaches include genetics, biophysics, cellular imaging, functional imaging, electrophysiology, or molecular biology. Candidates are expected to have demonstrated excellence and productivity in research and to participate in undergraduate and graduate teaching. The successful candidate will join an active research program in the Biology Department examining the cellular and molecular basis of behavior using genetic, behavioral and electrophysiological approaches and will be part of a strong research community at Penn in the School of Arts and Sciences and the Professional Schools, including Medicine. The Biology Department is broadly based in animal and plant molecular, cellular, developmental, and evolutionary biology and in ecology.

Applicants are encouraged to email their cover letter, CV, description of research interests and up to three reprints as pdf files to: **PennNeurobiologySearch @sas.upenn.edu** with Neurobiology in the Subject line. Alternatively, these documents may be sent to: **Neurobiology Search, Department of Biology, University of Pennsylvania, Philadelphia, PA 19104-6018**. Applicants at the Assistant Professor level should also arrange for at least three letters of reference to be sent to the email address above (as pdf files) or to the postal address. Review of applicants will begin in **November of 2006**.

The University of Pennsylvania is an Equal Opportunity/Affirmative Action Employer. Women and minorities are encouraged to apply.

FACULTY POSITIONS in Cancer Immunology, Vascular Biology, Cell Biology, Drug Development, and Genomics

The Sidney Kimmel Cancer Center is located in the center of the largest concentration of biotechnology companies and research institutes in the United States. The center focuses on developing new strategies in target discovery that impact cancer treatment. We are recruiting new faculty at all levels who will work in a new 96,000 sq ft research center opening in November, 2006.

Candidates should send their curriculum vitae and a list of three references to:

Albert B. Deisseroth, M.D., Ph.D.,
President & CEO
or
Jan Schnitzer, M.D.,
Sidney Kimmel Cancer Center

10835 Road to the Cure
San Diego, CA 92121

EOE

ASSISTANT PROFESSOR Biology and Management of Prokaryotic Plant Pathogens University of California, Riverside

The Department of Plant Pathology invites applications for a tenure-track faculty position emphasizing the biology, ecology, epidemiology or control of plant pathogenic bacteria. Knowledge of areas including disease diagnosis and management, vector biology, biocontrol, host resistance, molecular biology or genetics and genomics will be preferred. The position will join a vibrant community of faculty in the departments of Plant Pathology, Entomology and Botany and Plant Sciences, the Center for Plant Cell Biology, the Institute for Integrative Genome Biology and Cooperative Extension. The successful applicant will be expected to develop a strong, innovative, extramurally funded research program and contribute to undergraduate and graduate teaching in areas such as microbiology, plant pathology, pathogen-vector interactions or genomics. A Ph.D. and demonstrated research excellence are required. Review of applications will begin **December 15, 2006** and will continue until the position is filled. Applicants should submit a curriculum vitae, a statement of research and teaching interests, selected reprints and have three letters of reference sent to: **Dr. Katherine Borkovich, c/o C. Brusuelas, Department of Plant Pathology, 1415 Boyce Hall, 900 University Avenue, University of California, Riverside, CA 92521**. Email: **Cherylfb@ucr.edu**. Additional information can be found at **http://www.plantpathology.ucr.edu**.

The University of California is an Affirmative Action/Equal Opportunity Employer.

ANIMAL DEVELOPMENTAL BIOLOGIST

The Department of Biological Sciences at SUNY Brockport requests applications for a tenure-track position at the rank of Assistant Professor starting Fall 2007. The successful candidate will teach an upper-division course in developmental biology and appropriate undergraduate and graduate (M.S. level) courses in his or her area of expertise, and contribute to the teaching mission of the department. The candidate is also expected to develop an active research program in developmental biology, utilizing undergraduates and Master's students, and to seek external funding to support the research. We are particularly interested in persons who utilize a combination of cellular, molecular, and genetic approaches in studying development. A Ph.D. is required, and post-doctoral and teaching experience are highly preferred.

Applicants should apply on line at **www.brockportrecruit.org** and submit the following information: letter of application, curriculum vitae, copies of transcripts showing the highest degree awarded, and statements of teaching philosophy, research plans, and startup needs. All positions are subject to final budgetary approval.

Affirmative Action/Equal Opportunity Employer.

Department of Botany and Microbiology
University of Oklahoma

Applications are invited for three tenure-track positions to begin in August of 2007 at the Assistant Professor level. We will also accept applications from highly qualified individuals at the associate and full professor level through a complementary campus-wide Life Sciences Initiative (see Web-link below). The Department seeks outstanding individuals who will contribute to its research, teaching, and service missions, with specific research interests in: **(Search #1) Molecular Microbiology**, studying the molecular biology or genetics of microorganisms or microbial communities; **(Search #2) Microbial Physiology**, focusing on bioenergetics, enzymology, metabolic engineering, biofuels, or cell-cell interactions including biofilms; **(Search #3) Microbial Ecology**, investigating microbial interactions and their effects on the environment. All three positions should build on the department's strengths in anaerobic microbiology, global climate change biology, functional genomics, and microbial ecology.

Qualified candidates must possess a Ph.D., or equivalent degree, relevant postdoctoral experience, and provide evidence of a strong ability to develop independent, extramurally funded research as well as a commitment to teaching at the graduate and undergraduate levels. Applicants should send a current c.v., representative reprints, statements of research plans, teaching interests and philosophy, and the search # to which the application pertains, and arrange to have three confidential letters of reference sent to: **Dr. Gordon Uno, Chair, Department of Botany and Microbiology, 770 Van Vleet Oval, University of Oklahoma, Norman, OK 73019** (inquiries to **guno@ou.edu**). Review of applications begins **December 1, 2006** and will continue until positions are filled.

Successful candidates will have opportunities to collaborate with a growing and dynamic faculty. Resources include electron/confocal microscopy laboratories, a microarray facility, and a genome research institute. More information about the faculty, Department, and searches may be obtained at: **http://www.ou.edu/cas/botany-micro/**.

Women and members of under-represented groups are encouraged to apply. The University of Oklahoma is an Equal Opportunity Employer.

ASSISTANT PROFESSOR IN FRESHWATER FISH ECOLOGY
University of California, Berkeley

The Ecosystem Sciences Division of the Department of Environmental Science, Policy and Management (ESPM) at the University of California, Berkeley (**http://espm.berkeley.edu**) invites applications for a tenure-track, nine-month (academic year) faculty position in Freshwater Fish Ecology available starting July 1, 2007 (pending budgetary approval). The position includes a joint appointment in the California Agricultural Experiment Station. There are important interdisciplinary connections to the Department of Integrative Biology, Department of Earth and Planetary Science, and the Museum of Vertebrate Zoology.

Applicants should possess a Ph.D. in Fisheries, Ecology or a similar field. Strong skills in several of the following areas are desirable: population, community, or conservation ecology; and statistical or spatial analysis of ecological data. Candidates may conduct research on a variety of contemporary areas relating to fish ecology and environmental science such as human impacts on fisheries, sustainable fishery management practices, floodplain, estuary and riparian habitats, invasive species, toxics, habitat loss and change, conservation of aquatic biodiversity, river restoration, management of aquatic ecosystems, and provision of ecosystem goods and services. The candidate will be expected to teach an upper division course on Fisheries Biology and a graduate seminar annually, and occasionally participate in environmental science courses.

Electronic submissions are preferred as a single file and emailed to **freshwater@nature.berkeley.edu**. An application should include a curriculum vitae, statements of research and teaching interests, and recent publications. Three letters of recommendation should be mailed separately to: **Ms. Kim Oyler, Chair's Assistant, Freshwater Fish Ecology Search Committee, ESPM: Ecosystem Sciences Division, 137 Mulford Hall #3114, University of California, Berkeley, CA 94720-3114.** Refer potential reviewers to the UC Berkeley Statement of Confidentiality found at **http://apo.chance.berkeley.edu/evalltr.html**. Applications must be postmarked by **December 1, 2006**.

The University of California at Berkeley is an Equal Opportunity/ Affirmative Action Employer. We particularly encourage applications from women and under-represented ethnic minorities.

CHAIRMAN,
Department of Cell Biology
University of Oklahoma Health Sciences Center

Applications/nominations are invited for Chair of the Department of Cell Biology at the University of Oklahoma Health Sciences Center. This individual must be committed to the Department's mission of biomedical research in cellular, developmental, and molecular biology, as well as medical education. The successful candidate will have an M.D., Ph.D., or equivalent doctoral degree, qualify for tenured appointment as Professor, and be an internationally recognized leader in his/her area of research. Candidates with interests in cancer biology and diabetes are particularly sought, given the Department's participation in the ongoing expansion of the OU Cancer Institute and the Oklahoma Diabetes Center. Leadership positions in the OUCI are available for qualified applicants. With over $180 million in public and private support, OUCI represents the largest investment in biomedical research in the state's history. Please send a letter of application, curriculum vitae, the names and contact information for five references, plus a one-page summary that includes teaching philosophy and goals for maintaining and expanding the Department to: **Dr. Robert Foreman, Chair, Cell Biology Chair Search Committee, The University of Oklahoma, BMSB 653, 940 Stanton L. Young Blvd., Oklahoma City, OK, 73104 (http://w3.ouhsc.edu/cell%5Fbiology/)**. The review of applications will begin immediately and continue until the position is filled.

The University of Oklahoma is an Equal Opportunity Institution.

University Dean of Science,College of Science
National Central University, Taiwan, ROC

National Central University invites applications or nominations for the position of the Dean of the College of Science. The commencement date of the new deanship is expected to be not later than August 1, 2007, but an earlier date is preferred. The office has a three-year term, with a possibility to extend for another term.

The College of Science has five departments: Mathematics, Physics, Chemistry, Life Sciences, and Optics and Photonics; four graduate institutes: Statistics, Astronomy, Cognitive Neuroscience, and Systems Biology and Bioinformatics; about 120 full time faculty members; 920 undergraduates; and 800 Master and PhD students. It has been evaluated by the Ministry of Education to be one of the best colleges of science in Taiwan.

The successful candidate must have proven leadership and broad international perspectives, have been doing outstanding research in the natural or life sciences, hold or have held a full professorship or equivalent, and be able to communicate effectively in Mandarin. Government regulation requires that the successful candidate does not exceed 64 years of age.

Applicants or parties nominating candidates please send the candidate's resume, publication list and other relevant information, including the contact information of three references, before December 10, 2006, by mail or e-mail, to: Professor Y.H. Chang, Chair, Search Committee, College of Science, National Central University, 300 Jhongda Rd, Jhongli City, Taiwan 320, ROC. Please quote "**Subject: Dean of Science**". NCU homepage: **www.ncu.edu.tw/e_web/index.php**; Search Committee contact information: Email **cychiu@cc.ncu.edu.tw**, phone +886-3-4227151 ext. 65001, fax +886-3-4221210.

The National Institute of Allergy and Infectious Diseases, a major research component of the NIH and the Department of Health and Human Services, is recruiting a Staff Scientist. The position will be available in the Respiratory Viruses Section of the Laboratory of Infectious Diseases, and scientists with a M.D., D.V.M, or Ph.D. are eligible. The research activity involves (1) the development of live attenuated vaccines against potential pandemic strains of influenza and their evaluation in experimental animals as well as in clinical trials in humans; (2) examination of the pathogenesis of avian influenza viruses and SARS-coronavirus; (3) the evaluation of the immunologic determinants of resistance to infection and disease caused by influenza viruses and SARS-coronavirus. This full-time research position offers a unique opportunity to work on investigations that range from basic molecular biology to applied vaccinology. Staff Scientist applicants should have at least six years of laboratory work experience in molecular virology and vaccine research; the salary range is $73,178 - $165,195. Preference will be given to candidates who have experience working with avian influenza viruses. Applicants should submit their curriculum vitae, a letter of research interests, and names and addresses of three references to: **Kanta Subbarao, MD, MPH, Attn: A. LeCointe, NIAID, NIH, Bldg 50 Room 6234, MSC 8007, 50 South Drive, Bethesda, MD 20892-8007, FAX: (301) 496-8312, email: lecointe@niaid.nih.gov**

Review of applicants will begin on November 1, **200**6 and continue until a successful candidate is identified.

The National Institute of Allergy and Infectious Diseases, a major research component of the NIH and the Department of Health and Human Services, is recruiting a Staff Scientist. The position will be available in the Respiratory Viruses Section of the Laboratory of Infectious Diseases, and scientists with a M.D., D.V.M, or Ph.D. are eligible. The research activity involves (1) examination of the pathogenesis of pandemic and potential pandemic strains of influenza and their evaluation in vitro and in experimental animals; (2) influenza viral genomics, and examination of viral evolution in fitness and host adaptation; and (3) the development of influenza clinical trials in humans. This full-time research position offers a unique opportunity to work on investigations that range from basic molecular biology to clinical research. Staff Scientist applicants should have at least six years of laboratory work experience in molecular and classical virology research; the salary range is $73,178 - $165,195. Preference will be given to candidates who have experience working with avian influenza viruses and those with BSL3 experience. Applicants should submit their curriculum vitae, a letter of research interests, and names and addresses of three references to:**Jeffery K. Taubenberger, MD, PhD, Attn: D. Kyle, NIAID, NIH, Bldg 50 Room 6234, MSC 8007, 50 South Drive, Bethesda, MD 20892-8007, FAX: (301) 496-8312, email: dkyle@niaid.nih.gov**

Review of applicants will begin on **October 30, 2006** and continue until a successful candidate is identified.

NIDDK

Department of Health and Human Services
National Institutes of Health
National Institute of Diabetes and Digestive and Kidney Diseases

NIDDK POSTDOCTORAL POSITIONS within the Molecular and Clinical Hematology Branch are available to study hematopoiesis and hemoglobin switching. Current projects include studies of the molecular basis of lineage-specific differentiation of hematopoietic stem cells and the development of therapies for hemoglobinopathies and other genetic blood disorders. A strong background in molecular biology, cell biology and/or signal transduction is required. Opportunities exists to develop relevant clinical or translational projects. Salary and benefits will be commensurate with experience of the applicant. Interested candidates with an M.D. and/or Ph.D., and less than five years of postdoctoral experience should send a CV, bibliography, and names of three references to: **Griffin P. Rodgers, M.D. at (gr5n@nih.gov) or: Molecular and Clinical Hematology Branch, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 10 Center Drive, Building 10, Room 9N-119, Bethesda MD 20814**.

Senior Research Fellow Position
Cancer Biologist
Research Triangle Park, North Carolina

A Senior Research Fellow position is available at NIH/NIEHS to study the chemical-induced promotion of hepatocellular carcinoma (HCC). Emphasis will be placed on studies of the molecular mechanism of the nuclear receptor CAR-mediated development of HCC (Cancer Res. 64, 7197-7200, 2004), which examines the effects of altered gene expressions and of protein-protein interactions on cell growth/death and metabolisms, leading chemicals to promote HCC development. Research will also involve the use of state-of-the-art techniques including DNA microarrays and proteonomics. Applicants should possess a Ph.D. degree in Molecular Biology, Cell Biology, Biochemistry or Pharmacology, have a minimum of 3 years of relevant postdoctoral experience preferably in the areas of cancer research, and be able to successfully conduct, with minimal supervision, a pre-established program in laboratory research. Applicants must also have demonstrated outstanding scholastic achievement as evidenced by publications in high quality, peer-reviewed journals. Salary will be commensurate with qualifications and experience.

For prompt consideration, send cover letter, curriculum vitae, and three letters of reference to: **Masahiko Negishi, Ph.D, Senior Investigator, NIH/NIEHS, Division of Intramural Research, 111 T.W. Alexander Drive, Building 101, D236, Research Triangle Park, NC 27709, E-mail: NEGISHI@NIEHS.NIH.GOV**

WWW.NIH.GOV

Department of Health and Human Services
National Institutes of Health
National Institute of Allergy and Infectious Diseases

With nation-wide responsibility for improving the health and well being of all Americans, the Department of Health and Human Services oversees the biomedical research programs of the National Institutes of Health (NIH) and those of NIH's research Institutes.

The National Institute of Allergy and Infectious Diseases (NIAID), a major research component of the NIH and the Department of Health and Human Services, is recruiting for a Tenure/Tenure Track position in the Laboratory of Host Defenses (LHD). The LHD studies immune functions essential for host defense against infection (inherited immune deficiencies) and those required for immune homeostasis (autoimmunity associated with excessive inflammation). The LHD seeks an M.D. or M.D., Ph.D. physician scientist to develop an independent translational research program related to the genetic basis, pathophysiology, diagnosis and treatment of autoimmune diseases associated with excessive inflammation. An emphasis on clinical aspects of innate immunity including phagocytic cells, natural killer cells, dendritic cells and other antigen presenting cells, toll-like receptors or other pattern recognition receptors in its interface with acquired immunity is desirable. The applicant should have a strong track record of basic research of the genetic basis of disease and alterations in signaling pathways responsible for immune dysregulation. The applicant must possess expertise and experience in the design and conduct of diagnostic and therapeutic clinical trials studying and treating autoimmune diseases. Strong clinical credentials in a specialty area relevant to the proposed translational research program (relevant specialties include but are not limited to rheumatology, pulmonary diseases, hematology, immunology or infectious diseases) are required. The program of study proposed by the applicant must include both laboratory components and the conduct of clinical protocols to assess new diagnostic and therapeutic modalities to diagnose and treat autoimmunity associated with excessive inflammation. Applicants particularly suitable for this program are those who have knowledge and experience in the development and clinical application of novel biological agents including chemokines, soluble chemokine receptors, adenosine receptor agonists, monoclonal antibodies, cellular therapies including transplantation or gene therapy to correct the abnormalities in immunity, that achieve immune tolerance or to reduce abnormal inflammation.

The applicant must provide evidence in the submitted materials that the applicant has a current license to practice medicine in one of the states of the United States or must have all the credentials required by the State of Maryland for licensing to allow the practice of medicine. These credentials must include but are not limited to having a Doctor of Medicine or Doctor of Osteopathy degree from an accredited school in the U.S. or Canada, or a Doctor of Medicine or equivalent degree from a foreign medical school that provided education and medical knowledge substantially equivalent to accredited schools in the U.S. as demonstrated by permanent certification by the Educational Commission for Foreign Medical Graduates (ECFMG).

To be considered for this position, you will need to submit a curriculum vitae, bibliography, three (3) letters of reference, a detailed statement of research interests, and a hardcopy of selected publications to **Thomas A. Fleisher, MD, Chairperson, NIAID Search Committee, c/o Ms. Anissa N. Hunter, DIR Committee Coordinator, Reference Ad #009, 10 Center Drive MSC 1356, Building 10, Rm. 4A26, Bethesda, Maryland 20892-1356 or via e-mail at hunteran@niaid.nih.gov**. Completed applications **MUST** be received by **Thursday, November 15, 2006**. For additional information on this position, and for instructions on submitting your application, please see our website at: **www.niaid.nih.gov**.

Positions @ NIH

The National Institutes of Health

Postdoctoral Positions
National Institute of Child Health and Human Development

Developmental Neurogenetics
Sohyun Ahn, Ph.D., ahnsohyun@mail.nin.gov
http://gpp.nih.gov/Researchers/Members/NICHD/SohyunAhn.htm

Molecular Neuroendocrinologist, Melatonin and the Pineal Gland
David C. Klein, Ph.D., Dr. med. h.c., kleind@mail.nih.gov
http://eclipse.nichd.nih.gov/nichd/ldn/SNE/index.htm

Cellular Neurophysiologist
Dax Hoffman, Ph.D., hoffmand@mail.nih.gov
http://neuroscience.nihgov/Lab.asp?Org_ID=480

Mouse Models of Bone Dysplasia
Joan C. Marini, M.D., Ph.D., oidoc@helix.nih.gov
http://eclipse.nichd.nih.gov/nichd/annualreport/2005/bemb/bemb.htm

Infant ERP, Eye Movements, and Perception
Marc H. Bornstein, Ph.D., Marc_H_Bornstein@nih.gov
http://www.cfr.nichd.nih.gov

Neurophysiologist, Synaptic Plasticity and Neurotrophic Factors
Andres Buonanno, Ph.D., buonanno@mail.nih.gov
http://eclipse.nichd.nih.gov/nichd/annualreport/2005/smn/smn l.htm

Molecular Neuroscientist
Kuo-Ping Huang, Ph.D., huangk@mail.nih.gov
http://neuroscience.nih.gov/Lab.asp?Org_ID=364

Drosophila Developmental Neurobiologist
Chi-Hon Lee, M.D. Ph.D., leechih@mail.nih.gov
http://eclipse.nichd.nih.gov/nichd/lgrd/unc/index.htm

Reproductive Biologist/Developmental Biologist
Wai-Yee Chan, Ph.D., chanwy@mail.nih.gov
http://lcg.nichd.nih.gov

Mammalian Stem Cells and Embryonic Development
Heiner Westphal, M.D., hw@mail.nih.gov
http://eclipse.nichd.nih.gov/nichd/westphal/index.html

Applicants must have less than five years of postdoctoral experience.

Department of Health and Human Services
National Institutes of Health
Director, National Center for Research Resources and
Associate Director for Clinical Research (Extramural)

The Office of the Director, National Institutes of Health (NIH) in Bethesda, Maryland, is seeking applications from exceptional candidates for the position of Director, National Center for Research Resources (NCRR). The Director, NCRR, will also serve as the NIH Associate Director for Clinical Research (Extramural). NCRR, with a staff of approximately 100 employees and a $1 billion budget, is the focal point at NIH for biomedical, clinical and translational research resources. The incumbent serves as a principal advisor to the Director, NIH; participates in discussions relative to the development of major policy decisions affecting biomedical, clinical and translational research resources; provides advice and consultation to NIH components, advisory councils and grantee organizations and institutions; and assures that effective administrative procedures are established so that program operations and obligations of government funds and other resources are rendered consistent with statutory and regulatory requirements and within limitations imposed by the Department of Health and Human Services (DHHS) and Executive Branch policies. As Associate Director for Clinical Research (Extramural), the incumbent is expected to provide leadership for clinical research activities across the NIH. This leadership will involve the coordination of clinical research activities to enhance the integration of basic and clinical research. The Associate Director for Clinical Research will work closely with the other Institute and Center Directors to enhance the efficiency and effectiveness of clinical research supported by the NIH. Applicants must possess a Ph.D., M.D., or a comparable doctorate degree in the health sciences field plus senior level scientific experience and knowledge of biomedical, clinical and/or translational research programs in one or more health science areas. Salary is commensurate with experience and a full package of benefits (including retirement, health, life, long term care insurance, Thrift Savings Plan participation, etc.) is available. A detailed vacancy announcement, along with mandatory qualifications and application procedures, can be obtained via the NIH Home Page at: **http://www.jobs.nih.gov** under the Senior Job Openings section. Dr. Stephen Katz, Director, National Institute of Arthritis and Musculoskeletal and Skin Diseases, and Dr. David Schwartz, Director, National Institute of Environmental Health Sciences, will be serving as co-chairs of the search committee. Questions on application procedures may be addressed to **Ms. Regina Reiter at ReiterR@od.nih.gov or discussed with Ms. Reiter by calling 301-402-1130**. Applications **must** be received by **November 27, 2006**.

WWW.NIH.GOV

CANCER DIAGNOSIS PROGRAM
PROGRAM DIRECTOR
NATIONAL INSTITUTES OF HEALTH
NATIONAL CANCER INSTITUTE

The Cancer Diagnosis Program (CDP) is an extramural program within the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI) responsible for facilitating the translation of new knowledge in cancer biology and technologies into clinically useful diagnostic and predictive tests. CDP initiated the Program for the Assessment of Clinical Cancer Tests (PACCT) in 2000 to ensure that the next generation of biomarkers and laboratory tests improve the management of cancer patients. CDP works closely with other NCI units and with other government agencies that focus on related aspects of the diagnosis challenge. These include the Cancer Therapy Evaluation Program (CTEP), responsible for the NCI's clinical trials program; the Cancer Imaging Program, responsible for improvements in the non-invasive imaging of tumor physiology and biochemistry; staff from various programs involved in the development of state-of-the art informatics systems, and statistical and mathematical techniques adequate for the analysis of massive datasets; other components of the NCI; the National Institute of Standards and Technology; and such regulatory agencies as the FDA. Since the movement of new diagnostic and predictive tests into clinical practice also depends on interactions with the international oncology community, CDP also fosters collaborations with foreign oncology groups.

CDP is seeking an M.D., Ph.D. or D.O. to serve as a Program Director in the Diagnostics Evaluation Branch (DEB) to participate in a dynamic extramural research program of international scope. Experience with clinical trials and an interest in diagnosis and/or predicting the response to treatment, particularly as it relates to evaluation of biomarkers and in vitro diagnostic tools is necessary. The Program seeks an individual with experience in the translation of new knowledge and technology to clinical practice. A knowledge of systems biology and bioinformatics especially as it relates to identification of biomarkers or groups of biomarkers is helpful. Also helpful is experience that involves understanding the clinical decisions that can be informed by the use of markers and molecular technologies. The candidate will work with the Chief of the Diagnostics Evaluation Branch of the CDP and staff in the development of new initiatives for both the academic and business research communities. Significant effort will be devoted to projects initiated as part of PACCT.

Base salary for this position ranges from $91,407 to $118,828 per annum. MD and DO candidates are eligible for an additional allowance beginning at $13,000 per annum, depending on qualifications. Benefits include health and life insurance options, retirement, paid holidays and vacation leave.

To apply for this position, please visit: **http://jobsearch.usajobs.opm.gov/a9nih.asp** and keyword search for Vacancy Announcements **(VA), NCI-06-142673 (Ph.D.) or NCI-06-142674-DH (MD or DO)** for the mandatory application requirements. You must apply by the closing date of **October 30, 2006**. For questions about applying to the VA, please contact **Mary Lou Weathers, on (301) 402-5059 or weatherm@mail.nih.gov**.

For more information about the position, please contact **J. Milburn Jessup, MD at jessupj@mail.nih.gov or (301) 435-9010**.

Tenure Track Investigator
for Symptoms Management Laboratory

National Institute of Nursing Research, NIH

NINR seeks applications from nurse-scientists for a tenure-track or tenure-eligible position in its Symptom Management Laboratory. The successful applicant will be expected to establish an innovative independent research program in symptoms management in chronic or acute illness. Individuals with documented expertise in biobehavioral approaches to symptoms management research are of particular interest. Candidates must have a Ph.D. as well as advanced training and accomplishment in symptoms management research. The NINR Symptoms Management Laboratory offers unparalleled opportunities for multidisciplinary collaboration throughout NIH.

For additional information, contact **Renee G. Harris at harrisrg@mail.nih.gov**.

To apply, send your CV, cover letter including a summary of relevant experience, and the names and contact information for 3 recent references to: **Renee G. Harris, National Institute of Nursing Research, NIH, 10 Center Drive, CRC-East, Room 2-1339, Bethesda, MD 20892**. Applications will be accepted until the position is filled.

HIV and AIDS Malignancy Branch
Center for Cancer Research

Tenured/Tenure Track Position
Translational Researcher in Viral Oncogenesis

The HIV and AIDS Malignancy Branch (HAMB), NCI, is searching for a tenure-track or tenured investigator in the field of viral oncogenesis. It is anticipated that the investigator will establish an independent research program targeted to the study of the treatment, pathogenesis, and/or prevention of viral-induced tumors, especially those associated with AIDS. The research program should be translational in focus and be able to interface with a strong existing clinical research program in AIDS-related tumors. HAMB is located on the Bethesda campus of the NIH (http://ccr.cancer.gov/labs/lab.asp?labid=63). Current areas of research in HAMB focus on Kaposi's sarcoma-associated herpesvirus (KSHV /HHV -8)-associated tumors, the molecular biology of human papillomavirus (HPV), and the development of novel therapeutic interventions for HIV infection. Candidates for the position should have an M.D./Ph.D., Ph.D., or M.D. and strong research credentials. Applicants for this position should submit a curriculum vitae including bibliography, a statement of research interests, a two-page outline of the proposed research program, and the names of three references to **Chairman, Search Committee, HAMB, NCI, Attention Jan Huque, Building 10, Rm.10S255, 10 Center Drive, M.S.C. 1868, Bethesda, MD 20892-1868 no later than December 7, 2006**. You may also e-mail your application to: **huquei@mai1.nih.gov (Jan Huque, 301-435-4627)**.

Department of Health and Human Services
National Institutes of Health
National Institute of Environmental Health Sciences
Laboratory of Experimental Pathology
Research Triangle Park, North Carolina

Chief, Laboratory of Experimental Pathology/Senior Scientist
Veterinary Toxicologic Pathologist

The Division of Intramural Research, Laboratory of Experimental Pathology (LEP) is seeking a highly motivated veterinary pathologist with visionary leadership skills and expertise in toxicologic pathology to oversee the operation of the LEP. The LEP consists of 50 members and 7 groups including special techniques, molecular pathology, comparative pathobiology, clinical pathology, pathology support, laboratory animal management for the National Toxicology Program (NTP). The LEP provides pathology support for the NTP rodent toxicity and carcinogenicity studies as well as providing pathology support and collaboration for NIEHS intramural investigators. Management responsibilities include oversight and career mentoring of staff pathologists and scientists, trainees, and technical personnel and financial management and oversight of multiple pathology support contracts. The successful candidate is expected to insure state-of-the-science and timely pathology support to NIEHS scientists, maintain currency with evolving technologies and techniques appropriate for pathology core laboratory support, foster efficiency and increased effectiveness in support of the National Toxicology Program, and foster the advancement of toxicologic pathology research within and outside NIEHS.

Minimum qualifications include (1) DVM or equivalent veterinary degree, (2) specialty board certification in anatomic pathology by the American College of Veterinary Pathologists, and (3) minimum of 5 years demonstrated experience and qualifications as a toxicologic pathologist. Experience in molecular biology, small animal imaging, and/or a PhD degree are preferred.

For information about this position, contact **Dr. R. R. Maronpot at maronpot@niehs.nih.gov.** Salary will be commensurate with background and experience. Interested parties should submit a curriculum vitae, bibliography, brief statement of research interests and management experience, and arrange for three letters of recommendation to be sent to: **Mr. Will Williams (DIR-06-08), National Institutes of Health, National Institute of Environmental Health Sciences, P.O. Box 12233, Maildrop A2-06, 111 Alexander Drive, Room, A202, Research Triangle Park, NC 27709, e-mail: dir-appls@niehs.nih.gov**

Applications received by **December 31, 2006**, will receive first consideration. Applications received after that date will be considered on an as-needed basis until the position is filled. Applications from women and minorities are particularly encouraged.

Department of Health & Human Services (DHHS)
National Institutes of Health (NIH)
National Institute of Dental and Craniofacial Research (NIDCR)

The National Institute of Dental and Craniofacial Research (NIDCR), National Institutes of Health (NIH), Department of Health & Human Services (DHHS) is seeking applicants for a Biologist/Microbiologist/Health Scientist Administrator position in the Center for Integrative Biology and Infectious Diseases (CIBID). The position advertised is for the Director of the Microbiology Program. This program supports extramural basic and translational research on the role of oral microbes in health and disease. To this end, four broad scientific areas provide the basis for rapid development of knowledge of the etiology, pathogenesis, diagnosis, treatment and prevention of oral infectious diseases. These interrelated areas are: (i) Biofilms and Microbial Ecology; (ii) Microbial genomics; (iii) Microbial Virulence and Disease Pathogenesis; and (iv) Prevention and Treatment.

The incumbent will direct, administer and evaluate a portfolio of extramural grants, contracts and cooperative agreements and will stimulate interest in and provide advice to the extramural community regarding the respective research portfolio. In addition, the incumbent will participate in funding decisions, policy development, as well as implementation and coordination with other programs both within and outside of the NIDCR.

The salary range for this position is $77,353 to $118,828 per annum, commensurate with qualifications and professional experience. A full benefits package is available, which includes retirement, Thrift Savings Plan participation, health, life and long-term care insurance.

For qualifications required, evaluation criteria, and application instructions, view the vacancy announcements at: **http://jobsearch.usajobs.opm.gov/a9nih.asp**. Refer to announcement **# NIDCR-06-141634DE** or **NIDCR-06-147841MP**. Applications will be accepted until **October 27, 2006**. Please contact **Michelle Lipinski at 301-594-2286** or **lipinskim@od.nih.gov** if you have questions.

"Champions of Innovation." That's Pfizer Global Research and Development (PGRD). How did we earn such an esteemed reputation of excellence? By simply refusing to be intimidated by the challenges it takes to discover new cures and therapies for some of the world's most difficult diseases. To date, we've improved the lives of millions by bringing to market such outstanding medicines such as Lipitor, Zithromax, Viracept, Zoloft, and Viagra to name a few. But there is much more work to be done – and we can't do it without you. Your desire to positively impact our global society embodies the spirit of our people and our company.

OPPORTUNITIES IN ANALYTICAL R&D:

In Analytical R&D (ARD), we provide the St. Louis Global Biologic's team with analytical methods for the characterization and testing of biopharmaceutical products. This is accomplished by the skillful application of a variety of chromatographic, electrophoretic, spectroscopic and other analytical technologies. The Analytical group evaluates and integrates cutting edge analytical technology developed either in-house or acquired through strategic alliances.

Sr. Scientist/Process Development, Req #59265
Principal Scientist, Req #59270
Sr. Associate Scientist, Req #59273
Scientist/Sr. Scientist, Req #59275 (2 positions)

OPPORTUNITIES IN BIOPROCESS MAMMALIAN CELL R&D:

In Bioprocess R&D (BRD), we provide the St. Louis Global Biologic's team with mammalian and microbial cell based processes for large scale protein production. This is accomplished by the skillful application of a variety of molecular biology, cell culture, media development, fermentation, downstream purification and engineering technologies. The Bioprocess group evaluates and integrates cutting edge process development technology developed either in-house or acquired through strategic alliances.

Sr. Principal Scientist, Req #47889
Sr. Principal Scientist/Associate Fellow, Req #59564
Scientist/Sr. Scientist, Req #59568
Sr. Associate Scientist, Req #59569
Scientist/Sr. Scientist, Req #59570 (2 positions)

OPPORTUNITIES IN PHARMACEUTICAL R&D:

In Pharmaceutical R&D (PhRD), we provide the St. Louis Global Biologic's team with formulation development and drug product process technology for biopharmaceutical products. This is accomplished by the skillful application of a variety of pharmaceutical, formulation, and drug delivery technologies. The Pharmaceutical group evaluates and integrates cutting edge process formulation and delivery technology developed either in-house or acquired through strategic alliances.

Principal Scientist/Sr. Principal Scientist, Req #59263
Principal Scientist/Sr. Principal Scientist, Req #59274
Principal Scientist/Sr. Principal Scientist, Req #59277
Scientist/Sr. Scientist, Req #59280

At PGRD, you'll work alongside some of the most brilliant pharmaceutical professionals and have the opportunity to contribute to exciting and ground-breaking research. You'll also have access to unparalleled resources within a research driven environment where science, research, technology and instrumentation are the highest quality.

At PGRD we are committed to making the lives of our people better. So when you join us you can expect accolades for your contributions and commitment, and you'll earn a compensation and benefits package that are second to none. **For complete descriptions and to apply, please visit www.pfizer.com/careers and search the appropriate req number.**

Pfizer is proud to be an Equal Opportunity Employer and welcomes applications from people with different experiences, backgrounds and ethnicities.

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FELLOWSHIPS

Australian Government
National Health and Medical Research Council
N H M R C

INVESTING IN AUSTRALIA'S HEALTH

The New Australia Fellowships for Health and Medical Research

$AUD800,000 per annum for five years

Invitation to apply – funding to commence in 2007

The Australian Government has provided $AUD170 million over nine years to establish a pre-eminent award in health and medical research, the Australia Fellowship for Health and Medical Research (Australia Fellowship). This new Fellowship aims to attract and retain leading health and medical researchers.

The Australia Fellowship is for outstanding health and medical researchers across all disciplines. Applications are invited from leading researchers both in Australia and around the world.

In announcing this award, the NHMRC aims to:

- increase Australia's capacity for outstanding health and medical research at the highest competitive level internationally.
- encourage high calibre Australian researchers to continue their work in Australia.
- repatriate outstanding Australian researchers currently based overseas.
- attract leading international researchers to Australia, to benefit Australia through outstanding contributions to knowledge in health.
- further support the internationalisation of Australian health and medical research through enhancement of networks between the Australian and international research communities.
- enhance the reputation of Australia as a place of excellence in health and medical research.
- support the development of better health practice and policy, and the development of innovative industries in Australia.
- support the training of future health and medical researchers in intellectually stimulating environments.

Successful applicants will have leading international status in their fields and have proposed a research program of major impact and benefit to Australia.

Applicants who do not currently hold Australian permanent residency, or are not a New Zealand citizen who holds a Special Category Visa, will be required to obtain temporary resident status prior to commencement of an Australia Fellowship.

Applications for the first round of Australia Fellowships opened on 22 September 2006. The policy document and guide to applicants are available at:

www.nhmrc.gov.au/fellows/apply/granttype/career/index.htm

Applications close 5.00pm AEST 8 December 2006.

For further information on the Australia Fellowship scheme, email **research.fellowships@nhmrc.gov.au**

www.nhmrc.gov.au

POSITIONS OPEN

POSTDOCTORAL POSITION

UNIVERSITY OF CALGARY

A position is available immediately in the Airway Inflammation Group at the University of Calgary. The applicant will work in the laboratory of Dr. David Proud, Canada Research Chair in Inflammatory Airway Diseases to study the pathogenesis of rhinovirus-induced exacerbations of asthma and chronic obstructive pulmonary disease. The specific project will focus on the molecular mechanisms (transcriptional and post-transcriptional) by which Interleukin-17 profoundly modulates epithelial cell responses to rhinovirus infection. Expertise in cell culture/molecular biology would therefore be required.

Calgary is a vibrant, multicultural city (population 1,000,000) near the Rocky Mountains, Banff National Park and Lake Louise. This position is funded from external sources and is not a University of Calgary support staff position.

Interested candidates should send a CV and names of three references, preferably by email, to:

David Proud, PhD
Professor and Head
Department of Physiology & Biophysics, HSC 1626
University of Calgary
Calgary, Alberta T2N 4N1 Canada
Email: dproud@ucalgary.ca

In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada. The University of Calgary respects, appreciates and encourages diversity.

www.ucalgary.ca

Indian Institute of Science Education and Research

Professor / Associate Professor / Assistant Professor

Indian Institute of Science Education & Research (IISER) set up at Pune, India (**www.iiserpune.ac.in**) by the Government of India at par with IITs and IISc Bangalore offers a programme of five-year integrated Masters of Science in the Schools of Physical Sciences, Chemical Sciences, Life Sciences and Mathematics/ Information Sciences. In addition, there is a full-fledged research activity in a network arrangement with neighboring institutions. The teaching and research programmes have already started from 16th August 2006 at NCL Innovation Park adjacent to National Chemical Laboratory, Pune. The Institute invites applications from Indian nationals possessing excellent academic record and experiences in teaching and research for the following faculty at the levels of Professor, Associate Professor and Assistant Professor.

Qualifications: Ph.D in any area of Mathematics, Biology, Chemistry, Physics, Computer & System Sciences, Earth & Planetary Systems and Engineering Sciences with good post doctoral/ teaching and research experience, appropriate to the applied positions.

In addition to the regular pay, the faculty members will be provided with other perks such as communication expenses, book grant, membership to national/international professional societies, financial support to attend international conferences, sabbatical leave, leased housing etc. The institute will provide start up grants for research projects. **Please visit our website for further details**.

Interested candidate may apply enclosing: (i) Curriculum Vitae (ii) List of Publications (with reprints of important papers) (iii) Names and addresses (with e-mail address and fax number) of at least six referees (iv) Other details relevant to the candidature, including a statement of research purpose.

The Director, Indian Institute of Science Education Research (IISER), 900, NCL Innovation Park, Dr Homi Bhabha Road, Pune 411008, India

DuPont Central Research and Development

New Positions at DuPont

DuPont, a science-based company leading the introduction of biotechnology for industrial applications, is seeking Principal Investigators in several areas to join its Central Research and Development organization.

Organic Chemist / Polymer Chemist
Job Code: RES00455
The successful candidate will develop new specialty polymeric materials and formulations as part of a multidisciplinary team focused on medical devices and will be expected to translate customer requirements into concepts for new materials. The position is open to candidates with a Ph.D. in Organic Chemistry or Polymer Chemistry. Demonstrated knowledge of synthetic and mechanistic organic chemistry and/or polymer chemistry is expected. Experience with polymeric materials in medical applications is a plus.

Chemical Engineer – Polymers
Job Code: RES00456
The successful candidate will develop formulations and scale-up for new specialty polymers as part of a multidisciplinary team focused on medical devices. The individual will evaluate process options and conduct experiments to develop commercial processes that meet customer needs. The position is open to candidates with a Ph.D. in Chemical Engineering – Polymers. Demonstrated knowledge of polymer chemistry and chemical engineering principles of polymers is expected. Experience with polymeric materials in medical applications and cGMP background is a plus.

Chemical Engineer
Job Code: RES00458
The successful applicant will work in a multidisciplinary team primarily focused on the scale-up of biochemical and related processes. We are seeking a self-motivated, highly driven person to provide technical leadership and research output in a fast-paced environment. The chosen candidate will be expected to develop catalyst and process/separations technology for conversion of biochemical process outputs into useful intermediates for downstream products. Specifically, the successful candidate will be responsible for developing catalytic processes, evaluating process options, and conducting laboratory and pilot scale experiments necessary for the development of a commercial process. The position is open to candidates with a Ph.D. in Chemical Engineering with a demonstrated knowledge of chemical engineering principles for catalysis and process development.

Biochemical Engineer - Fermentation
Job Code: RES00457
This position involves development of microbial strain and fermentation process from bench through commercial scale. The successful applicant will have good communication, project management, and leadership skills as well as knowledge and experience in the areas of fermentation and microbial physiology. This position requires a multidisciplinary approach and a person who can take a leading role in microbial strain and fermentation process development within a collaborative team of molecular biologists, biochemists and engineers. The position is open to candidates with a Ph.D. in Biochemical Engineering and experience in microbial physiology, metabolic engineering and fermentation process development. Postdoctural experience preferred.

Biochemist/Enzymologist
Job Code: RES00460
We seek biochemists to work as part of an Industrial Biotechnology team developing fermentation and biocatalytic processes to make chemicals and materials. The role is to identify and characterize potential enzyme catalysts, then to troubleshoot and solve problems associated with the function of those enzymes in the process. The work may include improving native enzymes by carrying out directed evolution and designing and automating high throughput screens. Candidates must have advanced knowledge of biochemistry, emphasizing enzyme function, consistent with a Ph.D. in biochemistry, chemistry, or a related field, and 2+ years of postdoctoral training.

Molecular Microbiologist
Job Code: RES00459
This position involves engineering microbes (bacteria, yeasts, or fungi) for the economic production of industrial compounds, small molecules as well as macromolecules. The successful applicant will have expertise in molecular biology and genetics, microbial metabolism and biochemistry, and microbial physiology. Preference will be given to candidates with a broad knowledge base who will have demonstrated productivity in different research areas. Candidates should be self-motivated, thriving in a research team environment and committed to use biotechnology. The successful applicant will have a Ph.D. in Molecular Microbiology or a related field and a minimum of two years of postdoctoral training.

Qualified candidates should apply through DuPont's career web-page: www.dupont.com/careers. Click on: Jobs by region/United States/New Graduate Opportunities. Enter the job code as listed above in the keyword field. Use the new search button for successive searches.

DuPont is an Equal Opportunity Employer.

NSF-IGERT Opportunities at the University of Wisconsin-Madison

Graduate funding for students with a global environmental vision

Exceptional students interested in interdisciplinary and international environmental study are invited to apply for an NSF IGERT PhD Traineeship at the University of Wisconsin-Madison. These traineeships have a generous stipend, tuition waver, and health benefits. Opportunities are available in two different programs:

Biodiversity Conservation and Sustainable Development in Southwest China: Meeting the major challenges of biodiversity conservation and sustainable development requires understanding the interactions of biological, physical, social, and economic forces. IGERT trainees will address these issues by pursuing a PhD in one of over a dozen departments and participating in IGERT seminars, workshops, language training, and field research in the Himalayas of Yunnan, China - a "biodiversity hotspot." For more information, please visit **http://www.swchina.wisc.edu**. The application deadline for this program is **January 15, 2007**.

Certificate on Humans and the Global Environment - the CHANGE IGERT: To research problems of global environmental vulnerability, and solve them by promoting sustainable practices, researchers must learn how to analyze both qualitative and quantitative data. CHANGE IGERT fellows will acquire a new interdisciplinary graduate certificate that blends natural science, social science, and humanistic approaches at multiple scales from the global to the local. Fellows will receive training to foster successful interdisciplinary scholarship via a 'professional skills' module woven into the certificate curriculum. For more information, please visit **http://www.sage.wisc.edu/igert/**. The application deadline for this program is **January 2, 2007**.

THE UNIVERSITY of WISCONSIN MADISON

Maine Medical Center RESEARCH INSTITUTE

Scientist/Postdoctoral Position(s) - H601BL

Opportunities exist to assume a lead role in Institute-, NIH- and corporate-sponsored investigations of: 1/ erythroid progenitor cell development (including novel niche-specific Epo action modes, and response factors); 2/ newly discovered tyrosine and S/T kinases with hematopoietic suppressor activities; and 3/ the nature (and action mechanisms) of unique cell migration and adhesion factors involved in cytokine-dependent erythroid, megakaryocytic and myeloid progenitor cell development.

Approaches include new transgenic and knockout mouse models; systems for primary cell development ex vivo; transcriptome analyses and bioinformatics; and human CD34 cell & lentiviral RNAi systems. Opportunities also exist for participation in: studies of small molecule inhibitors & cytokine mimetics; & human patient samples/studies; and graduate & undergraduate teaching. Resources include subsidized cores in: Progenitor Cell Separation and Analysis; Genomics & Bioinformatics; Transgenic mouse construction; Lenti- and retro-virus production; Confocal microscopy; DNA & protein sequencing; Histopathology; and Small animal MRI.

Benefits, salary and resources are nationally competitive and positions are within the laboratory of DM Wojchowski at the Maine Medical Center Research Institute (www.mmcri.org). Please provide CV, statement of research interests, and professional reference contact information via resumes@mmc.org (or apply online at www.mmc.org).

The MaineHealth Family, EOE

UNIVERSITÄT LEIPZIG

Medical Faculty

The **Interdisciplinary Centre for Clinical Research (IZKF)** at the University of Leipzig invites applications for the Position of

Independent Research Group Leader

„Molecular Mechanisms of the Metabolic Syndrome"

to be funded up to BAT-O Ia level for a period of 5 years from 1st January 2007. Additional support is available for a post doctoral fellow (or two graduate students) and a technician, with an appropriate allowance for equipment and consumables.

The Centre is part of an interactive science network which includes the Biomedical-Biotechnological Centre (BBZ), the Coordination Centre for Clinical Studies (KKS) Leipzig, the Interdisciplinary Centre for Bioinformatics (IZBI), three Max-Planck-Institutes, the Environmental Research Centre Halle-Leipzig, the Fraunhofer Institute of Immunology and Cell Therapy (IZI) and the Bio-City Leipzig, which hosts lifescience start-ups.

The IZKF conducts research into cell-cell and cell-matrix-interactions relevant to diagnostic and therapeutic applications, focussing on the specialist areas of immunology, endocrinology, neurosciences and oncology. The new group should establish a clear, cell-based approach to research in the field of molecular endocrinology, cardiology or angiology, and will be expected to take advantage of the excellent opportunities for collaboration within the IZKF, and with the Clinical Research Group (KFO 152) "Atherobesity".

In addition to a doctoral qualification in medicine or the life sciences, applicants must have a strong background in a relevant field of cellular endocrinology, experimental animal research, molecular cell biology, a clear interest in clinically orientated research, and the ability to attract external funding.

Applications are to include CV, publication list, a summary of planned research and 2 letters of reference (to follow if necessary).

Applications should be submitted within **3 weeks** after the appearance of this advertisement to:

University of Leipzig
Medical Faculty
Bereich 4 Personal
Stephanstr. 9/C, D-04103 Leipzig

Further details are available from the IZKF-Office, phone: +49-(0)341-97 15940, e-mail: izkf@uni-leipzig.de, www.izkf-leipzig.de

Scientist/Senior Scientist position at the MCCF

The Molecular Cytology Core Facility (MCCF) uses tissue processing, *in situ* detection methods and optical microscopy to study the expression of molecular markers involved in normal development and in cancer. The MCCF adopts, develops and automates new methods, and maintains state-of-the-art-technology standards to serve the needs of the MSKCC investigators.

A Senior Research Scientist position is open in the Molecular Cytology Core Facility. We are seeking a highly-motivated, multi-disciplinary trained scientist, who will be able to implement all aspects of the research process at the Facility. The individual will interact with multiple researchers-users of the MCCF. Candidates with doctoral degree and solid background in developmental biology, cell biology or molecular biology are encouraged to apply. The candidate should have experience in immunohistochemistry/immunofluorescence, RNA *in situ* hybridization, optical microscopy, image acquisition and image analysis. This position offers a unique opportunity for a talented scientist to work in a dynamic and challenging environment at the heart of basic and translational research.

A minimum of 2-4 years of relevant research experience in academics or biotechnology are required. Candidates should have excellent communication skills, meticulous lab techniques and record keeping, and must be able to work in a highly collaborative manner.

Candidates should send their CV and three letters of references to: **Dr. Katia Manova, Molecular Cytology Core Facility, Developmental Biology Program, Sloan-Kettering Institute, MSKCC, 1275 York Avenue, Box 73, New York, NY 10021 or E-mail: k-manova@ski.mskcc.org.** EOE/AA

Memorial Sloan-Kettering Cancer Center
The Best Cancer Care. Anywhere.
www.mskcc.org

Mercer, Putnam and Farlow Fellowships in Plant Biology
Harvard University

The Arnold Arboretum of Harvard University and the Harvard University Herbaria invite applications for two year research fellowships in evolutionary biology, biogeography, systematics, development, ecology, genetics and physiology. Fellows are expected to pursue independent research projects, but must be sponsored by a research scientist or faculty member based at the Arnold Arboretum, Harvard University Herbaria, or Department of Organismic and Evolutionary Biology. The stipend is $40,000 per annum plus benefits, with up to $12,000 in additional funds for research expenses.

Putnam Fellowships are preferentially awarded for research using the living collections of the Arnold Arboretum. Mercer Fellowships are awarded for research on vascular plants. Farlow Fellowships are awarded for research on non-vascular plants and fungi.

Applications should contain: curriculum vitae, research proposal (8 single-spaced pages with 12-point font and 1-inch margins including a research budget); relevance of research to applicant's career goals; letter of support from a Harvard sponsor(s); and three letters of recommendation. Applications should be sent to: **Dr. Robert E. Cook, Director, Arnold Arboretum, 125 Arborway, Jamaica Plain, MA 02130**. For more information, see the Arboretum website at **www.arboretum.harvard.edu**. Review of applications will begin on **December 1, 2006**.

Max-Planck-Institut für extraterrestrische Physik

The Max-Planck-Institute for Extraterrestrial Physics (MPE) is establishing a new theoretical group with focus on the physics of galactic nuclei, lead by Prof. Andreas Burkert (University of Munich, USM). Research will focus on the various strongly coupled astrophysical processes that drive the evolution of galactic centers, their cycles of activity, the origin of Seyfert galaxies and Quasars, the growth of central supermassive black holes and the importance of these processes in shaping the Hubble Sequence. A strong interaction with the various observational and theoretical groups at USM and MPE is expected.

In this context, the MPE is seeking two or three ambitious, highly qualified

postdoctoral fellows

with expertise in computational and theoretical astrophysics. Experience in some of the following fields would be highly desirable: computational (magneto)hydrodynamics, stellar dynamics, radiation transport, interstellar matter, high energy astrophysics and galactic dynamics. Payment levels will be according to the Max Planck Society's guidelines for postdoctoral positions. Appointments are for 2 years, with a possible extension by one year, contingent upon satisfactory progress.

Evaluation of candidates will start in December 2006 but later applications will be considered until all free positions are filled. Further information about the MPE and the Computational Astrophysics Group at USM can be found at http://www.mpe.mpg.de and at http://www. usm.lmu.de/CAST/. The Max Planck Society is an equal opportunity employer. Applications from women, disabled people and minority groups are particularly welcome.

Interested candidates should send their application materials, including a curriculum vita, a summary of past and current research, provide the names of two referees willing to send letters of recommendation, and experience as well as future research interests to

University Observatory Munich
Prof. A. Burkert
Scheinerstr. 1, D-81679 Munich, Germany
(email: burkert@usm.uni-muenchen.de)

MAX-PLANCK-GESELLSCHAFT

POSITIONS OPEN

NEUROBIOLOGY
Keene State College

The Department of Biology at Keene State College invites applications for a tenure-track position at the **ASSISTANT PROFESSOR** level beginning fall 2007. The Department encourages applications from a diverse pool of candidates. To learn more about the School of Science and Social Science at Keene State College visit **website: http://www.keene.edu/science.**

The ideal candidate can teach a range of undergraduate courses including neurobiology and introductory biology; teach topical or interdisciplinary courses in Keene State College's new Integrative Studies Program for nonmajor students; and supervise undergraduate research. Qualifications: Require Ph.D. completed by August 1, 2007, in neurobiology or related field; a good general knowledge of biology; and some undergraduate teaching experience. Preference will be given to candidates with a strong commitment to undergraduate teaching, to liberal arts education, and to an integrated biological perspective; research experience with nonmammalian models; experience teaching integrated lecture and laboratory courses, or ability to teach cell biology, physiology, developmental biology, or anatomy. Knowledge of a specific animal group is desirable. Salary at the rank of Assistant Professor will be based on collective bargaining unit agreement, and was at $48,750 minimum in fall 2006.

For full consideration, submit letter of application, curriculum vitae, clear description of undergraduate teaching experience, statement of teaching philosophy/methods, statement of research interests, and three letters of reference (at least two addressing candidate's undergraduate teaching experience in some detail) to: **Neurobiology, FAC#20, Search Committee, Office of Human Resource Management, Keene State College, 229 Main Street, Keene, NH 03435-1604.** Review of applications will begin on December 1, 2006, and continue until position is filled.

Keene State College is a founding member of the Council of Public Liberal Arts Colleges, a national alliance of leading liberal arts colleges in the public sector. The College is accredited by the New England Association of Schools and Colleges and its education programs are National Council for Accreditation of Teacher Education-accredited. *As an Affirmative Action/Equal Opportunity Employer, Keene State College is engaged in an effort to build a community that reflects the diversity of society.*

TENURE-TRACK FACULTY POSITION
Inorganic/Materials Chemistry
Florida State University

The Department of Chemistry and Biochemistry at Florida State University anticipates an opening for a tenure-track **ASSISTANT PROFESSOR** position in the area of inorganic and materials chemistry to begin in fall 2007. Candidates are expected to demonstrate the ability to establish a highly creative interdisciplinary research program that is externally funded, and to contribute to the graduate and undergraduate teaching in the inorganic and materials program in the Department. The applicant's research interests can be drawn from any interdisciplinary materials/inorganic chemistry sub-area, including: biomaterials, nanoscience, energy, catalysis, bioinorganic chemistry, solid-state chemistry, organometallics, and/or development of state-of-the-art spectroscopic tools or methods applied to these areas. Applicants should send curriculum vitae, a description of their research plans, a statement of teaching philosophy and teaching interests, and arrange to have three letters of recommendation sent to the: **Chair of the Inorganic/Materials Search Committee, Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390.** Applications should be received by November 17, 2006, to ensure full consideration. *Florida State University is an Equal Opportunity/Affirmative Action Employer. Women, minorities, veterans, and disabled persons are encouraged to apply.*

FACULTY POSITION IN THE DEPARTMENT OF NEUROSCIENCES
Lerner Research Institute
The Cleveland Clinic Foundation

The Department of Neurosciences seeks outstanding candidates to fill several faculty positions. The search is focused at the **ASSISTANT, ASSOCIATE or FULL PROFESSOR** levels. Applicants must have a Ph.D. and /or M.D. and an active, independent research program that utilizes state-of-the-art techniques to investigate cellular and molecular aspects of neurobiology. Candidates with research programs in glial development, cortical development, synapse function, cell signaling, or pathogenesis of human central nervous system disease are encouraged to apply. Excellent Departmental facilities and generous startup funds are available. The Department of Neurosciences and the Lerner Research Institute **(website: http://www.lerner.ccf.org)** are undergoing rapid growth. The Department of Neurosciences has strong programs in developmental neurobiology, excitable membranes, and cell signaling. Interactions with clinical programs in movement disorders, Alzheimer's disease, and multiple sclerosis are plentiful.

Candidates should submit curriculum vitae, a list of publications, a brief statement of research interests, and three letters of reference to:

Bruce D. Trapp, Ph.D.
Department of Neurosciences NC30
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195

Affirmative Action/Equal Opportunity Employer.

PLANT EVOLUTIONARY BIOLOGIST
Department of Biology, Colorado State University
Website: http:// www.colostate.edu/Depts/Biology

The Biology Department invites applications for a tenure-track position **(ASSISTANT PROFESSOR)** in plant evolutionary biology to join a growing group of Evolutionary Biologists. We seek a broadly trained Plant Biologist who addresses fundamental and integrative questions in evolutionary biology. Applicants should be well-versed in genetics, with the possibility of applying genomic tools to organismal questions. Examples of appropriate research interests could include evolution of morphology and life histories, mating systems, population genetics and adaptation, hybridization and speciation, invasive species, and conservation biology. The successful candidate will be expected to develop an extramurally funded research program and contribute to undergraduate and graduate teaching.

Applicants must have a Ph.D. by the time of appointment; postdoctoral experience is preferred. To receive full consideration, apply online by November 8, 2006 **(website: http://www.natsci.colostate.edu/searches/Biology).** Include curriculum vitae, statements of research/teaching interests, representative publications, and the names and contact information for three referees. Referees will receive instructions by e-mail for submitting letters online, or may mail letters to: **Plant Evolutionary Biology Search Committee, Department of Biology, Colorado State University, Fort Collins, CO 80523-1878.** Complete applications of semi-finalists will be reviewed by all faculty in the Department.

Colorado State University is an Affirmative Action/Equal Opportunity Employer. Office of Equal Opportunity and Diversity, 101 Student Services.

THE COLLEGE OF WOOSTER

MICROBIOLOGIST. ASSISTANT PROFESSOR, tenure-track with ability to teach parts of introductory biology sequence, a nonmajors course in area of expertise, microbiology and another upper level course in biology. See description at **website: http://www.ohio5.org/faculty.htm** or contact **Dr. Dean Fraga, Chair, Department of Biology** at **telephone: 330-263-2557** or **e-mail: dfraga@wooster.edu.** *The College of Wooster is an Affirmative Action/Equal Opportunity Employer.*

PLANT DEVELOPMENT

The Plant Biology Department at the University of Georgia (UGA) has an opening at the **ASSISTANT PROFESSOR** level for a **PLANT DEVELOPMENTAL BIOLOGIST** interested in answering questions of fundamental importance to plant growth and development. Those who use comparative genomics approaches are particularly encouraged to apply. The successful candidate is expected to develop a vigorous externally funded research program. The Plant Biology Department has strengths in several areas and extensive links to other plant-related programs on campus; further information about the Department is available at **website: http://www.plantbiology.uga.edu.**

To apply, candidates should (1) combine a cover letter, curriculum vitae, short statements of research interests and teaching philosophy into a single PDF file; (2) three reprints of research papers should also be combined into a separate PDF file. These two files should then be submitted online at **website: http://www.plantbio.uga.edu/positions.html.** (3) Candidates should arrange to have four letters of recommendation submitted to the same website, or sent to: **Chairperson, Plant Development Search Committee, Plant Biology Department, Miller Plant Sciences Building, University of Georgia, Athens, GA 30602-7271.**

Applications received by 17 November 2006 are assured full consideration. *The Franklin College of Arts and Sciences is committed to increasing the diversity of its faculty and strongly encourages applications from individuals in underrepresented groups. UGA is an Equal Opportunity Employer.*

FACULTY POSITION IN MICROBIAL PATHOGENESIS
Department of Microbiology-Immunology
Northwestern University
Feinberg School of Medicine

A tenure-track position is open for a full-time faculty researcher (Ph.D., M.D./Ph.D. or M.D.) in the areas of microbial pathogenesis (bacterial and fungal), biodefense, immunobiology of microbial infections, or general microbiology. Rank is open, and salary is negotiable. All applicants should have substantial peer-reviewed publications that demonstrate research productivity and the ability to perform cutting-edge research. Candidates for an **ASSISTANT PROFESSOR** position should have postdoctoral research experience. Persons seeking appointment as **ASSOCIATE or FULL PROFESSOR** should have long-term research productivity and a history of grant support and academic service. Candidates should have an interest in teaching graduate and medical students. Starting date is negotiable after September 1, 2007. Application materials will be reviewed as received but, to receive full consideration, should be received by February 1, 2007. Please send complete curriculum vitae and the names and contact information of at least three references by **e-mail: micropath@northwestern.edu.**

Northwestern University is an Affirmative Action, Equal Opportunity Employer. Women and minorities are encouraged to apply. Hiring is contingent upon eligibility to work in the United States.

NATIONAL UNIVERSITY OF SINGAPORE
Department of Chemical and Biomolecular Engineering

The Department of Chemical and Biomolecular Engineering at National University of Singapore invites applications for **TENURE-TRACK FACULTY** positions at all levels. The Department is one of the largest internationally with excellent in-house infrastructure for experimental and computational research. A Ph.D. in chemical engineering or related areas and a strong research record with excellent publications are required. Please refer to **website: http://www.chbe.nus.edu.sg/** for more information on the areas of interest and for application details. Applicants should send full curriculum vitae (including key publications), a detailed research plan, a statement of teaching interest, and a list of names of at least three references to: **Professor Raj Rajagopalan, Head of Department (Attention: Ms. Nancy Chia, e-mail: nancychia@nus.edu.sg).**

2006 Salary Survey

A special *Science* editorial feature

Issue date
3 November 2006

Scientists are having a pretty good year in 2006. The median scientist got a 6.4% raise this year—well above inflation—comparing favorably to the rate of our last survey in 2004.

But money, it turns out, isn't everything: Our 3rd salary survey shows that salary is just one of many things that affect how well scientists like their jobs.

Be sure to read this editorial feature in the **3 November issue of *Science*** and online at **www.sciencecareers.org** after 3 November.

POSITIONS OPEN

ASSISTANT PROFESSORSHIPS IN BIOCHEMISTRY
Virginia Tech

As part of a University-wide expansion and enhancement of the molecular and biomedical life sciences, the Department of Biochemistry at Virginia Tech **(website: http://www.biochem.vt.edu)** is seeking applicants to fill two tenure-track positions at the rank of **ASSISTANT PROFESSOR.** We are seeking applicants who apply modern proteomic, kinetic, and/or spectroscopic tools to the study of protein structure-function relationships. Areas of particular interest include the regulation of protein function, the structural changes that characterize the protein life cycle, and/or mechanisms of enzymatic catalysis. The successful applicants will build and sustain an internationally recognized extramurally funded research program and participate in the instruction and advising of graduate and undergraduate students. Competitive salary, benefits, and start-up funds will be provided. Applicants should apply online, submitting curriculum vitae, research plan, and a statement of teaching interests to **website: http://jobs.vt.edu** (posting number 061080). Also, please arrange for three letters of reference to be sent to the: **Chair of the Search Committee, Professor Richard F. Helm (e-mail: helmrf@vt.edu), Department of Biochemistry, Fralin Biotechnology Center, Virginia Tech, Blacksburg, VA 24061.** Review of applications will begin on November 15, 2006. *Virginia Tech has a strong commitment to the principle of diversity and, in that spirit, seeks a broad spectrum of candidates, including women, minorities, and people with disabilities.*

FACULTY POSITIONS IN CHEMISTRY
University of Florida

The Department of Chemistry at the University of Florida announces a search for two tenure-track faculty members to begin in fall 2007. Candidates with research interests in the areas of macromolecular chemistry or bioanalytical or biophysical chemistry are invited to apply. For the macromolecular/polymer chemistry area, candidates at the **ASSISTANT or BEGINNING ASSOCIATE PROFESSOR** levels will be considered. For the physical, structural, or analytical methods applied to biological problems area, candidates at the **ASSISTANT PROFESSOR** level will be considered. In addition to contributing to the research, teaching, and service missions of the Department of Chemistry, we anticipate campuswide interactions in interdisciplinary programs with Departments in the Colleges of Liberal Arts and Sciences, Medicine and Engineering, along with other University-based Centers and Institutes. Applicants should submit curriculum vitae, description of their research plans (please specify either macromolecular or bioanalytical/biophysical in the cover letter), graduate/undergraduate teaching interests, and arrange to have three letters of recommendation sent on their behalf to the: **Faculty Search Committee, Department of Chemistry, P.O. Box 117200, University of Florida, Gainesville, FL 32611-7200,** on or before November 6, 2006. *The University of Florida is an Equal Opportunity Institution.*

The Department of Biochemistry, Duke University Medical Center, invites applications for **TWO FACULTY POSITIONS** at any level. We welcome candidates in all areas of biochemistry and biomolecular sciences, particularly in structural biology, membrane biochemistry, enzymology, and nucleic acids biology. Duke is undergoing considerable expansion of its efforts in these and related areas with the recent creation of the Institute for Biological Structure and Design, which is closely affiliated with the Department. The candidates will be expected to establish strong, independent research programs and to participate in departmental teaching. Send resume, summary of research interest, and three letters of reference to: **Christian R. H. Raetz, Department of Biochemistry. P. O. Box 3711, Duke University Medical Center, Durham, NC 27710.** Consideration of applications will commence in late November 2006. *Duke University is an Equal Opportunity/Affirmative Action Employer.*

POSITIONS OPEN

THE INSTITUTE FOR DIABETES, OBESITY, AND METABOLISM

The Institute for Diabetes, Obesity, and Metabolism (IDOM) at the University of Pennsylvania School of Medicine seeks candidates for **ASSISTANT and/or ASSOCIATE PROFESSOR** position in the tenure track. The faculty appointment will be in the appropriate Basic Science Department and/or the Department of Medicine in the School of Medicine. Rank will be commensurate with experience. Applicants must have a Ph.D. or M.D./Ph.D.

Qualified applicants must have demonstrated research productivity in either Type 2 diabetes or obesity. We are particularly interested in individuals who will complement existing strengths of the Penn IDOM. For more information, visit the IDOM **website: http://www.med.upenn.edu/idom/.** Qualifications and experience in teaching will be required.

An excellent space and startup package is available.

Please send curriculum vitae, letter of research interest, and three letters of reference to:

Mitchell Lazar, M.D., Ph.D.
Professor of Medicine and Chief of Endocrinology, Diabetes and Metabolism
Director, Institute for Diabetes, Obesity and Metabolism
c/o Ms. Kishani Martin
University of Pennsylvania School of Medicine
611 Clinical Research Building
415 Curie Boulevard
Philadelphia, PA 19104-6149

The University of Pennsylvania is an Equal Opportunity, Affirmative Action Employer. Women and minority candidates are strongly encouraged to apply.

PROFESSORSHIPS in the Department of Medicinal Chemistry, University of Kansas. The University of Kansas is seeking highly qualified candidates for two positions in the Department of Medicinal Chemistry. Qualified candidates for either position will have a Ph.D. or equivalent degree in medicinal chemistry, chemistry, natural product chemistry, or a closely related field. It is expected that one appointment will be made at the **ASSISTANT/ASSOCIATE PROFESSOR** level and one at the **ASSOCIATE/FULL PROFESSOR** level. All candidates should provide curriculum vitae, summary of research interests, and funding history (if applicable) in their application. Assistant Professor candidates should arrange for at least three letters of reference to be sent at the time of application. Highly qualified candidates for an appointment at the Associate or Full Professor levels should supply the names of at least three individuals familiar with their qualifications. Preference will be given to applicants whose research interests complement those of the current faculty; candidates in the fields of natural product chemistry and synthetic medicinal chemistry are especially encouraged to apply. More information about the Department and complete position descriptions are available at **website: http://www.medchem.ku.edu.** Application materials should be sent to: **Professor Jeffrey Aubé, 1251 Wescoe Hall Drive, Malott Hall, Room 4070, Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66045.** *Review of applications begins on November 6, 2006, and will continue until the positions are filled. The University of Kansas is an Affirmative Action/Equal Opportunity Employer.*

The Department of Biology at Missouri State University anticipates an August 2007 opening for a tenure-track **ASSISTANT PROFESSOR** in microbiology. Review of applications begins 15 November 2006. See **website: http://missouristate.edu/academicopenings** for a full description of the position. Direct further inquiries to **John Steiert, e-mail: johnsteiert@missouristate.edu, telephone: 417-836-6916.** *Equal Opportunity/Affirmative Action.*

POSITIONS OPEN

BIOCHEMISTRY TENURE-TRACK POSITION
Bowdoin College

The Chemistry Department and Biochemistry Committee seek applicants for a joint tenure-track appointment in chemistry and biochemistry beginning fall 2007. A Ph.D. in chemistry or biochemistry is required and postdoctoral research and teaching experience are desirable. While this appointment is anticipated at the **ASSISTANT PROFESSOR** level, under exceptional circumstances individuals may be considered for appointment as **ASSOCIATE PROFESSOR.** The successful candidate must possess a strong commitment to undergraduate education and demonstrate the potential to develop an active and productive research program that involves undergraduates. Teaching responsibilities (three courses per year) will include core biochemistry courses (including contributions to the laboratory course in molecular biology and biochemistry) and contributions to the Department curriculum at the introductory and advanced levels. Bowdoin College is a highly selective, coeducational undergraduate liberal arts college located two and a half hours north of Boston on the Maine coast. Further information about Bowdoin and the Department is available at **website: http://academic.bowdoin.edu/chemistry/.** Applicants should send curriculum vitae, a statement of research plans, a statement on teaching philosophy, and arrange for three letters of recommendation to be sent to: **Jeff Nagle, Chair, Department of Chemistry, 6600 College Station, Bowdoin College, Brunswick, Maine 04011-8466.** Review of applications will begin 30 October 2006, and continue until the position is filled. *Bowdoin College is committed to equality through Affirmative Action and is an Equal Opportunity Employer. We encourage inquiries from candidates who will enrich and contribute to the cultural and ethnic diversity of our college. Bowdoin College does not discriminate on the basis of age, race, creed, color, religion, marital status, gender, sexual orientation, veteran status, national origin, or disability status in employment, or in our education programs.*

TENURE-TRACK FACULTY POSITIONS
Molecular Medicine and Genetics
Wayne State University School of Medicine

Multiple tenure-track positions at the **ASSISTANT, ASSOCIATE, or FULL PROFESSOR** levels are available as part of a multiyear hiring plan by the Center for Molecular Medicine and Genetics (CMMG). The Wayne State University (WSU) School of Medicine recently completed a $20 million renovation of the CMMG laboratory and core research facilities. To fill this new space, we are recruiting outstanding candidates holding Ph.D., M.D., or M.D.-Ph.D. degrees to join an active faculty conducting basic and translational research in systems biology, genomics, comparative genomics, neuroscience, computational biology, mitochondrial biology, and medical genetics. Joint appointments in clinical departments are available for Physician-Scientists. The CMMG **(website: http://www.genetics.wayne.edu)** offers extensive opportunities for collaboration both within the Center and throughout the University. Wayne State scientists have excellent opportunities to develop translational research with industry, government, and other academic institutions. Significant startup funds are available. Wayne State University is Michigan's only research University located in an urban setting. Applications will be reviewed upon receipt and continued until all positions have been filled.

Applications should include a letter of application, curriculum vitae, and the names and addresses of at least three references and be sent to: **Ms. Mary Anne Housey, Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Room 3127 Scott Hall, 540 E. Canfield Street, Detroit, MI 48201.**

WSU is a premier Institution of higher education offering more than 350 academic programs through 14 schools and colleges to more than 31,000 students in metropolitan Detroit.

WSU is an Equal Opportunity/Affirmative Action Employer.

The Debiopharm Life Sciences Award 2006 in oncology goes to Dr Eduard Batlle !

On October 11, 2006, Dr Eduard Batlle* from the Institut de Recerca Biomèdica of Barcelona, Spain received the Debiopharm Life Sciences Award for his outstanding research in fundamental and clinical oncology.

His achievements include research leading to the following publications: "Snail as a suppressor of E-Cadherin gene expression in epithelial cells", "The genetic program driven by beta-catenin and Tcf in colorectal cancer (CRC). Revealing the role of EphB receptors in the intestinal epithelium" and "EphB receptors as suppressors of CRC progression".

The Award ceremony which took place at the Ecole Polytechnique Fédérale de Lausanne (EPFL) in Switzerland, during the 6th annual ISREC Conference On Cancer Research, was funded by Debiopharm and co-organised by the EPFL and the Swiss Institute for Experimental Cancer Research (ISREC). With this nomination, Dr Batlle and his laboratory received CHF 100'000, a certificate and an etched crystal tribute commemorating this honor.

The objective of the Debiopharm Life Sciences Award is to mentor and motivate young innovative European researchers in the field of life sciences, with a focus this year on oncology. Potential candidates for the Award are required to be under the age of 40, with research having therapeutic and industrial potential. Selection criteria include novelty and originality of the work, as well as its importance and significance in connection with targeted therapeutic fields.

The topic for the Debiopharm Life Sciences Award 2007 is NEUROSCIENCE

EPFL ÉCOLE POLYTECHNIQUE FÉDÉRALE DE LAUSANNE
ISREC Institut Suisse de Recherche Expérimentale sur le Cancer
DEBIOPHARM LIFE SCIENCES AWARD

* Dr Batlle is a Group Leader and ICREA Researcher at the Applied and Translational Oncology Program, Colorectal Cancer Laboratory

FACULTY POSITIONS

BIOTECHNOLOGY TENURE-TRACK FACULTY POSITION
University of Toronto at Mississauga

The Department of Biology at the University of Toronto at Mississauga invites applications for a full-time, tenure-track appointment in biotechnology at the **ASSISTANT PROFESSOR** level starting July 1, 2007. The successful applicant will have a Ph.D. and preferably postdoctoral experience, an outstanding academic record, and demonstrated excellence in research and teaching. The successful candidate must have a strong background in molecular biology, structural biology, or genomics, and will be expected to develop an internationally recognized research program combining basic and applied investigation with active collaboration with industrial partners. Teaching will include participation in graduate and undergraduate courses according to his/her area of specialization. Salary will be commensurate with qualifications and experience.

Applications will be accepted until December 1, 2006. Applicants should provide curriculum vitae, statement of teaching philosophy and interests, an outline of their proposed research, and should arrange to have three confidential letters of recommendation sent on their behalf to: **Professor Robert Reisz, Chair, Department of Biology, University of Toronto at Mississauga, Mississauga, Ontario, Canada L5L 1C6. E-mail: rreisz@utm.utoronto.ca.** For more information on the Department go to **website: http://www.utm.utoronto.ca/~w3bio/homepage/.**

The University of Toronto is strongly committed to diversity within its community and especially welcomes applications from visible minority group members, women, Aboriginal persons, persons with disabilities, members of sexual minority groups, and others who may contribute to the further diversification of ideas. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority.

ASSISTANT PROFESSOR
Field Crops Pathology

The Department of Plant Pathology at the University of Wisconsin, Madison, invites applications for a 12-month tenure-track faculty position at the Assistant Professor level. The position will focus on pathology of field (agronomic) crops and carries a 75 percent extension/25 percent research distribution of effort. The incumbent will be expected to develop progressive, externally funded extension and research programs that improve the management of diseases of field crops while protecting soil, water, and other natural resources. The incumbent will mentor graduate and undergraduate students and support the Department's teaching mission. Requirements include: a Ph.D. in plant pathology or related discipline; a strong foundation in the principles and concepts of plant pathology and relevant research experience; effective oral and written communication skills, including the ability to use modern delivery technologies to reach diverse audiences; and a positive attitude for teamwork, including the ability to lead and motivate others. For a complete description of the position, see our **website: http://www.plantpath.wisc.edu.** To apply, submit curriculum vitae; a cover letter with a statement of extension and research interests; a copy of undergraduate and graduate transcripts; and three letters of reference to: **Professor Patricia McManus, Department of Plant Pathology, 1630 Linden Drive, Madison, WI 53706-1520.** Applications received by November 27, 2006, will be assured full consideration; review of applications will continue until a suitable candidate is identified. *The University of Wisconsin is an Equal Opportunity/Affirmative Action Employer.*

Additional job postings not featured in this issue can be viewed online at **website: http://www.sciencecareers.org**. New jobs are added daily!

POSITIONS OPEN

THE BUSINESS OF MARINE BIOTECHNOLOGY FELLOWSHIPS
University of North Carolina, Wilmington

The Center for Marine Science at the University of North Carolina Wilmington (UNCW) is offering three exceptional **RESEARCH FELLOWS** in marine biotechnology. Candidates must have a Ph.D. in a biotechnology-related area and are expected to conduct research in marine science laboratories at the University while pursuing a professional M.B.A. degree in the University's Cameron School of Business. The goal of this 24-month program is to produce individuals with a solid science background as well as the business skills needed to prosper in a modern competitive business environment. Students in the M.B.A. portion of the Program will master the core functions of business, develop analytical and quantitative business skills, and study current and future business issues through real world experiences with regional companies involved in marine biotechnology. Excellent verbal and written skills are required.

The research portion of the program generally involves working in one of three focus areas: (1) Bioassay technique development focusing on novel sensing methods with particular application in the marine environment; (2) Finfish mariculture which may include reproduction, genetics and selective breeding, larval physiology, nutrition, health and disease management, recirculating aquaculture technology, and commercial demonstration; and (3) Marine pharmaceuticals and nutraceuticals from cultured organisms, bioengineered natural products, novel enzymes and biosynthetic pathways. Candidates should clearly identify their interests in one of the three focus areas in their cover letter. Candidates with interests in other biotechnology-related areas will be considered based on the strength of their application. Selected candidates would receive salary and benefits including health insurance and retirement contributions for 24 months. Position title will be Visiting Research Assistant Professor. Tuition for the coursework necessary to obtain the M.B.A. is also provided.

Screening of the applicants will begin December 15, 2006, and applicants will be invited to join the program April 1, 2007, and will be required to start May 1, 2007. All degree requirements must be met by May 1, 2007, to qualify for the Fellowship. Letter of application, curriculum vitae, summary of research plans, and names and addresses of three references should be sent via the online application process available on the web at **website: http://consensus.uncw.edu**, not e-mailed or mailed. Microsoft Word or Adobe PDF attachments are strongly preferred. For questions regarding the online applications process, contact **Jody Smith** at **telephone: 910-962-2330.** For questions regarding the positions or the Center, contact **Dr. Ronald K. Sizemore** at **e-mail: sizemorer@uncw.edu** or visit our **website: http://www.uncw.edu/cmsr.** *UNCW conducts criminal background checks on finalists prior to offers of employment. UNCW is an Equal Opportunity, Affirmative Action Employer. Minorities and women are encouraged to apply.*

FACULTY POSITIONS

Mercer University School of Medicine in Macon, Georgia, invites applications for a 12-month, salaried, tenure-track position in biochemistry at the rank of **ASSISTANT PROFESSOR.** The successful candidate must have a commitment to excellence in education in a case-based, multidisciplinary, medical curriculum and is expected to develop an independent research program capable of attracting external funding. Expertise in intermediary metabolism is desirable. Applicants should have a doctoral degree from an accredited university/college in biochemistry or equivalent with at least three years of postdoctoral training. Applications should be submitted online at **website: https://www.mercerjobs.com.** *Affirmative Action/Equal Opportunity Employer/ADA.*

POSITIONS OPEN

CAREER OPPORTUNITY

This unique program offers the candidate with an earned doctorate in the life sciences the opportunity to obtain the Doctor of Optometry (OD) degree in 27 months (beginning in March of each year). Employment opportunities exist in research, education, industry, and private practice. Contact the **Admissions Office, telephone: 800-824-5526** at **The New England College of Optometry, 424 Beacon Street, Boston, MA 02115.** Additional information at **website: http://www.neco.edu, e-mail: admissions@neco.edu.**

POSTDOCTORAL POSITION funded by NIH grants to study integrin and insulin-like growth factor 1 signaling in chondrocytes. Must have Ph.D. and/or M.D. degree, strong background in molecular biology and/or cell signaling, and good communication skills. Send curriculum vitae and names of three references to: **Dr. Richard F. Loeser, Molecular Medicine, Wake Forest University School of Medicine, Winston-Salem, NC 27157; e-mail: rloeser@wfubmc.edu.** *Wake Forest University School of Medicine is an Equal Opportunity, Affirmative Action Employer.*

MARKETPLACE

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Apply Now!
The application deadline for the 2007-2008 Fellowships is 20 December 2006. Fellowships are awarded in the spring and begin in September. Stipends range from $67,000 to $87,000, depending on experience.
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Allison Smith, PhD

Psychology, University of Michigan.

2004-2006 AAAS Fellow at the U.S. Department of Homeland Security, Science and Technology Directorate, Threat Awareness Portfolio.

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